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CLINICAL SIGNIFICANCE OF THE RHEUMATOID SERUM FACTOR

BY

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Many human sera can be shown to contain a factor or factors which enhance certain antigen–antibody reactions; but this activity is present in relatively high titre in the serum of patients with rheumatoid arthritis. Since the report of Rose *et al.* (1948) sheep erythrocytes suspended in non-agglutinating doses of anti-sheep-erythrocyte serum have been used extensively to titrate this rheumatoid serum factor, but other sensitized particles such as bacteria (Wager, 1950), polystyrene latex (Plotz and Singer, 1956), and bentonite (Bozicevich *et al.*, 1958) may be employed. The results obtained with these various agglutinating systems indicate that they can provide a more or less reliable and specific aid to the diagnosis of rheumatoid disease (Ziff, 1957; McEwen *et al.*, 1958).

Neither the mechanism of agglutination nor the nature of the rheumatoid agglutinating factor is fully understood. It is thought that the rheumatoid factor combines with a γ-globulin component (of human or animal origin) attached to the particle; and a diagnostic test based on the precipitation which occurs between rheumatoid serum and γ-globulin (Cohn fraction II) from human plasma pools has been proposed (Epstein *et al.*, 1956). The agglutinating activity of rheumatoid serum is located mainly in the γ-globulin fraction; it may be concentrated by various chemical fractionation procedures (Ziff, 1957), by elution from agglutinated erythrocytes (Greenbury, 1956), and by ultracentrifugation (Franklin *et al.*, 1957), and by this last method the agglutinating activity has been shown to be associated with a γ-globulin of unusually high molecular weight.

In the routine titration of the rheumatoid agglutinating factor, some workers have preferred to use serum fractions rather than whole serum; and it would appear from published results that these offer some advantages as regards sensitivity and specificity (Svartz and Schlossmann, 1954; Hess, 1956; Ziff *et al.*, 1956). In our hands such serum fractions have not proved more active serologically than the whole serum from which they were derived. Partly because of this and partly because we wished to collect sufficient data for meaningful analysis, we have, since 1948, continued to use the same method in both hospital practice and population surveys. The results of clinical trials up to 1950 (Ball, 1952) were based on titres recorded after incubation for one hour; but further experience has shown that the titres recorded after 18 hours' incubation give results which are more closely related to the clinical findings, so that the results of the 18-hours test have been used throughout the present analysis.

Method

The method uses sensitized sheep erythrocytes, the sensitivity of which is controlled by a series of human sera of known agglutinating activity. Different batches of haemolysin at a constant agglutinating or haemolytic dose often yield identical titres with a given human serum; sometimes small but definite differences occur, and rarely the differences may be very large. We have therefore found it necessary to arrive at the appropriate dilution of sensitizing antiserum by trial and error, using standard human sera as controls (Ball, 1950).

Whole human serum is inactivated and absorbed with normal sheep cells before titration. The titre is read after incubation for one hour at 37° C. and again after refrigeration overnight at 4° C. (approximately 18 hours).

The titre of a patient's serum tends to remain remarkably constant over a period of weeks or even months and bears no close relationship to the E.S.R. or clinical assessments of disease activity in the untreated or treated case (Ball, 1952; Ziff, 1957). In most cases the results of the sheep cell agglutination test (S.C.A.T.) remain rather constant over longer periods of time, and two illustrative cases are shown in Fig. 1.

Case 1 was a man aged 39 with severe nodular rheumatoid arthritis of six months' duration on admission to hospital. His agglutinating titre, tested on 32 occasions over a period of 18 months, remained consistently high. Case 2 was a man aged 30 with atypical spondylitis of five years' duration; he developed severe involvement of all his peripheral limb joints and bilateral uveitis, and finally died from atlanto-axial dislocation, but his agglutinating titre, tested on 20 occasions over 18 months, remained persistently low. Occasionally, however, agglutinating titres do fluctuate substantially, as shown in Cases 3 and 4, both of which had definite rheumatoid arthritis of six months' duration when first tested. In Case 3, a man aged 45, the S.C.A.T. was strongly positive on admission but became negative for a period during the fourth year of his disease, when he was readmitted to hospital because of a severe allergic dermatitis; whereas in Case 4, a woman aged 42, borderline S.C.A.T. titres initially rose to high levels during the third year of her disease, when she was readmitted for an exacerbation of her arthritis, and then became negative for a time during the fifth year. Both these cases developed articular erosions but neither had nodules.

From such examples it is clear that occasional negative tests occur in definite cases of rheumatoid arthritis at

some stage of their disease, but too few of our patients have been tested routinely at regular periods of time irrespective of the state of their disease for us to be able to make any statement about the behaviour of the test during periods of remission and exacerbation of the disease.

Such studies have been carried out by de Forest *et al.* (1958) on a small number of patients and they found

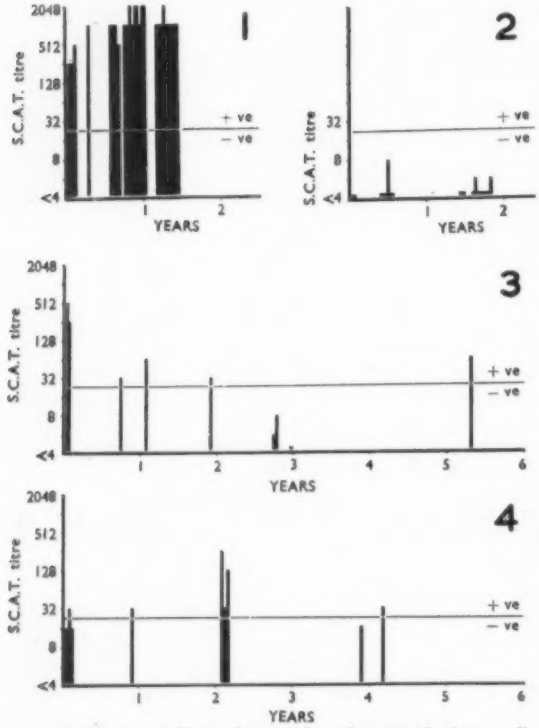

FIG. 1.—Histogram illustrating results of repeated sheep cell agglutination tests in four patients suffering from: (1) severe nodular rheumatoid arthritis; (2) spondylitis with severe peripheral joint involvement; (3) and (4) rheumatoid arthritis without nodules.

15 with rheumatoid arthritis in whom the test converted from positive to negative several months after the onset of complete remission of the disease process; in four of these the test became positive again for a time during a recurrence of disease activity.

Many of the cases considered in this paper were not serially tested, so that in analysing our material we have mainly dealt with the results obtained at the first test in each case.

Material

Since 1949 all patients admitted to the rheumatism beds in the Manchester Royal Infirmary have had their sera tested routinely at weekly intervals during their stay in hospital. Patients attending a special spondylitis clinic have also had their sera tested routinely at least once, but since 1951 only selected patients attending other clinics have had their sera tested. Many tests have also been done on sera from in-patients under the care of other physicians and surgeons at the infirmary. Many of these patients had been seen in consultation by the staff of the rheumatism centre, and results from a few of these patients have been included to enlarge certain diagnostic groups that would otherwise have been rather small.

Sera collected during field surveys have also been studied. These were taken both from random samples of the general population (Kellgren and Lawrence, 1956) and from samples selected by clinical screening for arthritis (Miall *et al.*, 1953, 1958; Miall, 1955).

Results

During the years 1952–7, 790 patients were admitted to the rheumatism beds of the infirmary. In Table I the results of the first in-patient S.C.A.T. are compared with

TABLE I.—*Total In-patients, 1952–7: First In-patient S.C.A.T. Result, Original Diagnosis*

Diagnosis	Total No.	Positive	
		No.	%
Definite rheumatoid arthritis ..	393	340	87
Probable " " ..	41	28	68
Juvenile " " ..	15	6	40
Diffuse collagen diseases ..	78	40	51
Other arthritides	229	23	10
Bone diseases	18	2	11
Miscellaneous diseases	16	2	12.5
Total	790	441	56

the clinical diagnoses recorded in each case before S.C.A.T. results became available. In arriving at this diagnosis *x*-ray films of the joints, and laboratory tests such as E.S.R., blood count, and occasionally other tests such as serum uric acid, L.E. cells, etc., were taken into account as well as the clinical features of the case.

In 393 patients the initial diagnosis was definite rheumatoid arthritis, and in 87% of these the S.C.A.T. was positive at the first test. In 41 patients rheumatoid arthritis was recorded as the diagnosis once in the out-patient clinic or on admission to the ward but some alternative diagnosis was recorded on the other occasion. These cases have been classed as probable rheumatoid arthritis, and positive tests were found in 68% of this group. Patients in whom polyarthritis began before the age of 15 years are classed as juvenile rheumatoid arthritis. Although some of them were young adults at the time of testing, only 40% of this small group had positive tests. This lower proportion of positive tests in juvenile rheumatoid arthritis has been observed by others, and indeed our figure of 40% is remarkably close to the 38% quoted by Ziff (1957) in 69 cases collected from the literature.

The term "diffuse connective-tissue diseases" is used to indicate conditions such as systemic lupus erythematosus, systemic sclerosis, and polyarteritis nodosa, and it will be seen that positive tests were found in 51% of the 78 patients in this category. 229 patients were recorded as suffering from other forms of arthritis, and of these only 10% gave positive tests. There was a small group of 18 patients with various metabolic diseases of bone. The two patients who had positive tests in this group were suffering from malacia due to familial vitamin D resistance and Paget's disease respectively. Finally there were 16 patients with miscellaneous non-articular diseases, amongst whom there were two positive tests.

In Table II are shown the results obtained during the period 1949–50. At this time all out-patients were tested routinely, and some 90% of the cases shown in this table were in fact seen only as out-patients. There is another important difference in that prior to 1951 our working definition for rheumatoid arthritis included all inflammatory polyarthritis for which no other cause could be demonstrated. In 1951 our working definition

TABLE II.—*Mainly Out-patients, 1949–50: First S.C.A.T. Result, Original Diagnosis*

Diagnosis	Total No.	Positive	
		No.	%
Rheumatoid arthritis	642	327	51
Diffuse collagen diseases ..	23	6	26
Other arthritides	941	45	5
Bone diseases	26	0	0
Miscellaneous diseases	291	4	1
Total	1,923	382	20

of rheumatoid arthritis was changed to include only polyarthritis which might be expected to be associated with a positive S.C.A.T. (Kellgren, 1952). Amongst the patients who were seen only as out-patients there were naturally many with relatively trivial disease in whom the diagnosis was also less certain, and this together with the change in our diagnostic criteria probably accounts for the striking difference between the results in Tables I and II. The figures shown in Table II refer to the results of the S.C.A.T. read at 18 hours, as do all other results in this paper. They therefore differ slightly from the results of the test read at one hour that were published previously (Ball, 1952). It is, however, interesting to note that amongst the patients with rheumatoid arthritis tested during 1949–50 there were 96 with subcutaneous nodules and that 80 (83%) of these were positive in the 18-hours test.

Rheumatoid Arthritis

Further details of the 393 patients with definite rheumatoid arthritis admitted to the wards during 1952–7 are shown in Table III. Subcutaneous nodules were recorded as present in 39% of these cases, and a positive S.C.A.T. was obtained in 100% of the 62 males and 92% of the 91 females with nodules. This confirms

TABLE III.—*Definite Rheumatoid Arthritis: In-patient S.C.A.T. Results, 1952–7*

Nodules	Males			Females			Both Sexes		
	Total No.	Positive		Total No.	Positive		Total No.	Positive	
		No.	%		No.	%		No.	%
Original Diagnosis—First Test—Any Duration									
Nodular	62	62	100	91	84	92	153	146	95
Non-nodular	87	73	84	153	121	78	240	194	81
Total	149	135	90	244	205	84	393	340	87
Original Diagnosis—First Test—Duration under 1 Year Only									
Nodular	7	7	100	7	5	71	14	12	86
Non-nodular	22	14	64	28	19	68	50	33	66
Total	29	21	72	35	24	69	64	45	70
Revised Diagnosis—Highest Test—Any Duration									
Nodular	62	62	100	90	87	97	152	149	98
Non-nodular	83	77	93	147	130	88	230	207	90
Total	145	139	96	237	217	92	382	356	93

our earlier observation of the close association between the rheumatoid serum factor and the necrobiotic rheumatoid nodule.

In 64 patients the disease was of less than one year's duration on admission to the ward. Nodules were present in 14 of these early cases and the S.C.A.T. was positive in 45 (70%). In such early cases the diagnosis is necessarily less certain in some instances and as a result of subsequent developments can occasionally be shown to have been incorrect.

All the in-patients in whom a diagnosis of rheumatoid arthritis had been recorded but whose sera gave persistently negative tests were reviewed in a follow-up study by Dixon (1958). At this follow-up examination the original diagnosis of rheumatoid arthritis was shown to have been incorrect in 11 of the patients in this series. For instance, one woman with polyarthritis and nodules was later shown to be suffering from reticulohistiocytosis, and two other patients had developed psoriasis.

If such cases are excluded and the highest titre recorded is taken instead of the results of the first test, the proportion of positive tests in our definite cases of rheumatoid arthritis becomes 96% for males and 92% for females, a proportion which compares well with other published results using the same test or modifications of it (Heller *et al.*, 1949 ; Pike *et al.*, 1950 ; Hobson and Gorrill, 1952 ; Svartz and Schlossmann, 1952 ; de Forest *et al.*, 1956), or other agglutinating systems (Heller *et al.*, 1952 ; Svartz and Schlossmann, 1954 ; Jacobson *et al.*, 1956 ; Ziff *et al.*, 1956 ; Hess, 1956 ; Plotz and Singer, 1956 ; Craig *et al.*, 1957 ; Singer and Plotz, 1958).

Diffuse Connective-Tissue Diseases

Our findings in this group are shown in Table IV, which includes a few patients seen only as out-patients

TABLE IV.—*Diffuse Connective-Tissue and Vascular Diseases: In-patients and Out-patients, 1949–57. First S.C.A.T. Result —Original Diagnosis*

Diagnosis	Total No.	S.C.A.T. Positive		Mean Age	Females	
		No.	%		No.	%
Systemic lupus erythematosus ..	41	17	41	38	36	88
Systemic sclerosis and scleroderma	39	16	41	40	32	82
Digital endarteropathy ..	25	11	44	46	22	88
Dermatomyositis	16	2	13	34	12	75
Polyarteritis nodosa without R.A.	11	0	0	36	6	55
Polyarteritis nodosa with R.A.	4	3	75	52	1	25

and also those seen in consultation with other physicians as well as the patients listed in Tables I and II.

Systemic Lupus Erythematosus.—Sera from 41 definite cases were tested, and 17 (41%) of them gave a positive S.C.A.T. During the earlier years reliable tests for L.E. cells were not available to us, so that the diagnosis had to be based on clinical findings and the results of other laboratory tests. Of 16 later cases in which L.E. cells were found, eight gave positive tests. Among those in which the S.C.A.T. was positive, articular and/or peripheral vascular lesions were prominent, whereas in patients without this lesion, such as those in whom the disease affected mainly the skin and kidneys or other viscera, the S.C.A.T. was often negative.

Systemic Sclerosis.—Positive tests were obtained in 16 (41%) of 39 cases. As in lupus erythematosus, high agglutinating titres tended to be associated with vascular and articular lesions, and negative tests were found in patients who only had scleroderma.

Digital Endarteropathy.—This group of patients consisted predominantly of adult females who developed rapid occlusion of the digital and other arteries associated with mild constitutional illness at the onset. They had severe Raynaud's phenomenon and nutritional lesions of the finger pulps, but they had no diffuse sclerosis and no articular lesions. Most of these patients came to us from the neurovascular surgical clinic, and some patients of this type were referred to by Jepson

(1951) as examples of a form of Raynaud's syndrome peculiar to middle-aged females. One of these patients with a positive S.C.A.T. died of right heart failure secondary to presumed pulmonary hypertension, and at necropsy arterial lesions of the type shown in Fig. 2 were found in both digital and pulmonary arteries. Wade and Ball (1957) have published details of three further cases of unexplained pulmonary hypertension associated with a positive S.C.A.T. Similar arterial lesions have been reported in patients with systemic sclerosis (Masugi and Yä-Shu, 1938; Moore and Sheehan, 1952) and also in patients with rheumatoid arthritis (Bywaters, 1957). The S.C.A.T. was negative in all of 10 sera from patients with juvenile obliterative arteritis of Buerger's type kindly provided for us by the neurovascular clinic, and it is also usually negative in other vascular diseases. It is therefore possible that the form of arteropathy shown in Fig. 2 as well as the rheumatoid nodule may be associated with positive S.C.A.T.

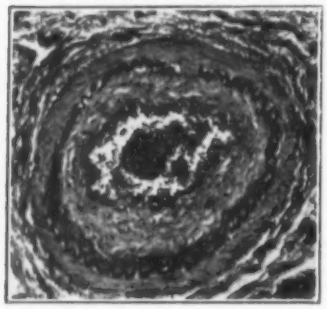

FIG. 2.—Section of artery showing concentric intimal fibro-elastosis, preservation of media and elastica, and absence of inflammatory cellular infiltration. (×115.)

Dermatomyositis.—Only two positive results were obtained among 16 cases tested. Thus in dermatomyositis the S.C.A.T. was usually negative. In most instances the diagnosis presented no difficulty, but there were one or two patients in whom the alternative diagnosis of systemic lupus erythematosus was seriously considered at some stage, and this might account for the occasional positive test in this group.

Polyarteritis Nodosa.—The results of the S.C.A.T. in this group depend on whether the polyarteritis occurs independently or as a complication of severe rheumatoid arthritis (Ball, 1954). Amongst the 11 patients without rheumatoid arthritis in whom the diagnosis of polyarteritis nodosa was confirmed either by biopsy or by necropsy the S.C.A.T. was uniformly negative, so that this type of arterial disease is also not associated with a high agglutinating titre.

In summary it may be said that a positive S.C.A.T. was found in nearly half the patients with systemic lupus erythematosus or systemic sclerosis, and also in patients who had only the arterial lesions sometimes found in these and certain other syndromes; but in patients with dermatomyositis or polyarteritis nodosa and other miscellaneous arterial diseases the S.C.A.T. is rarely positive.

Other Arthritides

Our results in a variety of polyarthritic syndromes are presented in Table V. In nearly all these conditions the proportion of positive results in the S.C.A.T. is very low and does not differ from what may be expected in a random sample of the general population in the North-west of England (see Table VII). Some comments on diagnostic definitions and the nature of the cases included in Table V are, however, required.

TABLE V.—*Other Selected Diseases: In-patients and Out-patients, 1949–57. First S.C.A.T. Result—Original Diagnosis*

Diagnosis	Total No.	S.C.A.T. Positive		Mean Age	Females	
		No.	%		No.	%
Rheumatic fever	59	3	5	28	43	73
Ankylosing spondylitis	537	23	4	36	98	18
Atypical ankylosing spondylitis	129	16	12	38	23	18
Valvular heart disease with spinal arthritis	21	0	0	37	13	62
Psoriasis and arthritis	62	11	18	44	34	55
Gouty arthritis	57	4	7	54	9	16
Rheumatoid polyarthritis with hyperuricaemia	6	6	100	49	2	33
Reiter's disease	52	4	8	39	7	13
Atypical polyarthritis	31	4	13	44	23	74
Pulmonary osteoarthropathy	6	1	17	61	0	0
Osteoarthrosis	283	18	6	57	222	78
Neuropathic arthropathy	5	1	20	54	3	60
Disk lesions	57	1	2	47	30	53
Tuberculous arthritis	23	1	5	33	9	39
Gonococcal	4	0	0	25	2	50
Shoulder syndromes	19	1	5	52	15	79
Erythema nodosum	3	0	0	33	0	0
Intermittent hydrarthrosis	6	0	0	37	4	67
Acromegaly	14	0	0	31	5	36
Osteochondritis	9	0	0	34	3	33
Marfan's syndrome	3	0	0	18	2	66
Morquoi's	3	0	0	23	1	33
Alkaptonuria	1	0	0	53	1	100
Behcet's disease	2	0	0	38	0	0
Total	1,392	94	6·7	42	549	39

For rheumatic fever we have used the usual criteria, and our cases mainly represent patients with acute or subacute polysynovitis with active rheumatic heart disease. A high proportion of the patients were, however, adults, so that our group is not a truly representative sample of patients with rheumatic fever, which is predominantly a disease of childhood.

The 537 cases of ankylosing spondylitis represent typical cases (Sharp and Easson, 1954; Sharp, 1957). Amongst the 129 atypical cases there were a few that undoubtedly had rheumatoid arthritis with major spinal involvement, and in some of these cases the correct diagnosis has become apparent in later years; but these have been included as spondylitis, since in Table V the original diagnosis is being compared with the results of the first S.C.A.T. performed. A detailed analysis of limb-joint involvement in relation to the S.C.A.T. has been carried out by Sharp for the patients seen by him in the spondylitis clinic during the years 1952–3. This is shown in Table VI. In this analysis the highest titre recorded in multiple tests was used instead of the results of the first test. It will be seen that some form of limb-joint involvement was common even in the typical cases but that peripheral joint involvement was observed only in some 31% of the typical cases, though it was the rule in atypical cases. Only 2 out of 37 typical cases with peripheral joint involvement and only 5 out of 27 atypical cases with peripheral joint involvement had positive tests, so that a high agglutinating titre is not

TABLE VI.—*Spondylitis Series, 1952–3*

S.C.A.T. Result and Limb Joints Involved	Typical			Atypical			Total
	M	F	Total	M	F	Total	
S.C.A.T. positive	5	4	9	6	2	8	17
Limb joints involved	3	1	4	6	1	7	11
*Peripheral limb joints involved	2	0	2	4	1	5	7
S.C.A.T. negative	108	15	123	31	1	32	155
Limb joints involved	67	9	76	23	1	24	100
*Peripheral limb joints involved	30	5	35	21	1	22	57
Total patients	113	19	132	37	3	40	172

* Knees and elbows and all joints distal to these were classed as peripheral.

specially associated with peripheral joint involvement as such but appears to be related more to the type of joint involvement. In this respect our findings agree with those of other workers as reported by Ziff (1957).

Progressive valvular heart disease with spinal arthritis is a category that requires further definition. Patients in this group had recurrent episodes of polyarthritis affecting both limb joints and spine, with a marked tendency to spinal ankylosis. The heart lesions, which were predominantly aortic, progressed with each episode of arthritis. Three patients with this syndrome also had all the features of recurrent Reiter's disease, and have been included under that head, but in the 21 remaining cases there was no clue to the nature of the disease process. In past publications from this centre these patients have been classed as examples of chronic rheumatic fever (Thomas, 1955; Sharp, 1957), but the detailed anatomical studies of similar cases reported by Clark *et al.* (1957) make this hypothesis no longer tenable. On the other hand, the uniformly negative results of the S.C.A.T. in this group are strong evidence against their being cases of rheumatoid disease with cardiac involvement. We have therefore used the non-committal descriptive term of progressive valvular heart disease with spinal arthritis.

The category of psoriasis and arthritis contains all our patients with inflammatory and erosive polyarthritis who also were recorded as having psoriasis and whose sera were tested. Two of these cases also had nodules, and a small number of the patients in this group appeared to have typical rheumatoid arthritis, but in the great majority the arthritis had distinctive characteristics and the S.C.A.T. was negative. Many patients with typical psoriatic arthropathy were not tested, so that there is an excess of patients with possible rheumatoid arthritis amongst the 62 that were tested. If we allow for this selection, our findings are in general agreement with those of Wright (1957) and other workers as reported by Ziff (1957), and in practice we distinguish psoriatic arthropathy from rheumatoid arthritis, a distinction we have found useful in the management of individual patients.

The majority of our 57 cases of gouty arthritis had severe gout with chronic joint involvement, and tophi, and all had hyperuricaemia of over 6 mg./100 ml. In this group there were only four positive tests, which is in agreement with the findings of others (Ziff, 1957).

There were, however, six patients with typical rheumatoid arthritis in whom hyperuricaemia was an unexpected laboratory finding. In these cases synovial biopsy and other detailed investigations were carried out to establish the correct diagnosis. The S.C.A.T. was positive in all six, which suggests that hyperuricaemia as such does not inhibit this reaction.

The 52 cases of Reiter's disease were all definite cases. Although the majority were recurrent or chronic cases, the S.C.A.T. was positive in only four.

The category of atypical polyarthritis has been used for patients with chronic inflammatory polyarthritis affecting mainly the larger limb joints and spine but in whom there were none of the radiological signs of spondylitis. The nature of the arthritis in these patients is at present obscure; but the S.C.A.T. is rarely positive in this type of case, so that we do not classify them as rheumatoid arthritis.

The remaining diagnostic categories need no comment.

In summary our findings agree very closely with those of other workers, and the low proportion of positive tests in most of the polyarthritic conditions shown in Table III is strong evidence against these conditions being varieties of rheumatoid disease as we define it.

Uveitis

Uveitis has often been regarded as a feature of rheumatoid disease. In adults uveitis is an important feature of both spondylitis and Reiter's disease but is rarely seen in nodular rheumatoid arthritis (Stanworth and Sharp, 1956).

The S.C.A.T. was performed in 190 patients with uveitis attending the Manchester Royal Eye Hospital. Positive results were obtained in only 10 (5%), and 6 of these had clinical evidence of rheumatoid arthritis. There does not therefore appear to be any association between uveitis and the rheumatoid serum factor.

Population Studies: Random Samples

In the course of epidemiological studies of rheumatoid disease the S.C.A.T. has been determined in sera from a 1 in 10 random sample of all individuals in the age group 55–64 years in the Lancashire town of Leigh, which has a population of approximately 48,000. These individuals also had a comprehensive clinical and radiological examination (Kellgren and Lawrence, 1956). The proportion of sera showing agglutination at each dilution is shown in Fig. 3, and it will be seen that there

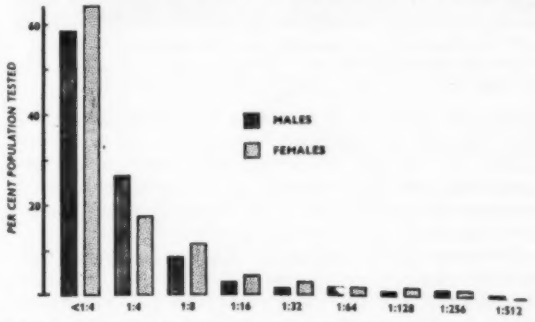

FIG. 3.—Distribution of sheep cell agglutinating titres in sera from a random sample of an urban population aged 55–64 years. The sample contained 163 males and 187 females. (Reproduced from *Ann. rheum. Dis.*, 1956, **15**, 3.)

TABLE VII.—*Clinical and Radiological Evidence of Rheumatoid Arthritis in 19 Individuals With a Positive S.C.A.T. From Random Sample of Population Aged 55–64*

Evidence of Rheumatoid Arthritis	No. of Individuals
Definite clinical and radiological rheumatoid arthritis ..	5
,, ,, rheumatoid arthritis only	3
,, radiological rheumatoid arthritis only	2
Possible clinical rheumatoid arthritis	4
No rheumatoid arthritis recorded	5

is remarkably little difference between the two sexes. Of the 350 individuals tested, 163 were males, 8 (5%) with positive tests, and 187 females, 11 (6%) with positive tests. The clinical and radiological findings in the 19 individuals with positive tests are shown in Table VII. Of these, eight had definite clinical rheumatoid arthritis, a further four had clinical symptoms or signs suggestive of rheumatoid arthritis, but in the remaining seven no clinical evidence of rheumatoid arthritis was recorded. However, in two of these individuals definite radiological signs of rheumatoid arthritis were present—in the feet in one case and in the cervical spine in the other. In another

small random sample from South Wales two further individuals were encountered with a positive S.C.A.T. in whom the only signs of rheumatoid arthritis were radiological changes in the cervical spine. This finding led to a detailed investigation of the radiological and pathological features of rheumatoid arthritis of the cervical spine in adults (Ball, 1958; Sharp, Purser, and Lawrence, 1958).

In established cases of rheumatoid arthritis being treated in hospital the following radiological appearances were characteristically found: narrowing of multiple disks, especially the upper ones, a tendency to subluxation, and a lack of accompanying osteophytosis (Fig. 4). In a random population sample of 428

FIG. 4.—Radiograph of cervical spine in flexion and extension showing multiple subluxations. Woman aged 51 with nodular rheumatoid arthritis of five years' duration; S.C.A.T. 1:512.

individuals aged 55–64 radiological appearances of this type showed a significant association with positive results in the S.C.A.T., but they were often not associated with other clinically recognizable evidence of rheumatoid arthritis. In clinical practice we have also been struck by the frequency, especially in elderly men, with which severe radiological changes of rheumatoid arthritis may be found in the feet of patients who state that they have never experienced pain or disability in the feet. It would thus appear that a proportion of positive tests in the S.C.A.T. may be associated with rheumatoid changes in the joints which may be either symptomless or of such a nature that they would not be generally recognized as rheumatoid by current criteria. Apparently false-positive results in the S.C.A.T. should therefore be accepted with reserve, at least in the 55–64 age group. The details of the five individuals from the Leigh sample with apparently false-positive tests are set out in Table VIII, from which it will be seen that at least three of them had significant signs of joint disease which may well have been rheumatoid in nature though they were not so regarded at the time of the survey.

The study in Leigh has been extended by Lawrence to a 1 in 30 sample of all individuals of over 25 years of age and, although the complete material has not yet been analysed, the results of the S.C.A.T. are shown in Table IX. From this it will be seen that positive tests were obtained in 5.7% of the 1,165 individuals tested, the proportion of positive tests being somewhat higher at certain ages and lower at others. In the younger age groups clinical and radiological evidence of rheumatoid arthritis will certainly have a lower prevalence, which raises the question of the significance of these positive tests in the younger individuals.

In a study of the relatives of propositi with positive S.C.A.T. obtained from the random sample of Leigh, Lawrence and Ball (1958) found 19 positive tests amongst 94 available blood relatives, a proportion of 20%, which is far greater than the 5.7% found in the population as a whole. Similar results have been reported by Ziff *et al.* (1958), who found positive inhibition tests in 20% of 140 relatives of 46 propositi with rheumatoid arthritis, although only two positive results were obtained with the direct euglobulin agglutination test. The rheumatoid serum factor would therefore appear to show a significant degree of familial aggregation. No such increased prevalence of positive tests has so far been observed in a small sample of spouses tested. Thus a positive S.C.A.T. may well be an index of some inherited biochemical characteristic which predisposes the individual concerned to certain types of disease, and a high prevalence of both clinical

TABLE IX.—*S.C.A.T. Results by Sex and Age Group in 1 in 30 Random Sample of the Adult Population of Leigh*

Age Group	Males					Females				
	Sample No.	Tested No.	Positive			Sample No.	Tested No.	Positive		
			No.	% of Tested	% of Sample			No.	% of Tested	% of Sample
15–24 ..	55	48	0	0	0	65	56	2	4	3
25–34 ..	131	113	5	4	4	115	98	5	5	4
35–44 ..	127	103	2	2	2	148	119	4	3	3
45–54 ..	169	146	9	6	5	171	140	11	8	6
55–64 ..	102	88	4	5	4	139	101	6	6	4
65+	91	75	11	15	12	115	78	7	9	6
Not stated ..	6	—				5	—			
Total ..	681	573	31	5·4	4·6	758	592	35	5·9	4·6

TABLE VIII.—*Features of Five Individuals from Random Sample Aged 55–64 with Positive S.C.A.T. in Whom No Evidence of Rheumatoid Arthritis was Recorded at the Time of Survey*

Case	Sex and Age	S.C.A.T.	Radiological Findings				Symptoms	Clinical Signs of Joint Disease	Clinical Diagnosis
			Rheumatoid Arthritis		Osteoarthrosis				
			Grade	Site	Grade	Site			
190	M 57	1/256	None	—	Slight	Hands, feet, spine	Lumbago one attack; pain in hip	Back, reduced curves, limited motion, vasospasm	Disk degeneration
215	M 55	1/64	Doubtful	Feet	None	—	Recurrent lumbago; few days' pain in arms	Crepitus in shoulders, limited lumbar spine, vaso-spasm, sweating	Osteoarthrosis and disk degeneration
300	M 60	1/32	None	—	,,	—	None	Contracture palmar fascia	Dupuytren's contracture
333	M 60	1/64	Doubtful	Hands	Slight	Knees, spine	After crush injury to feet, 5 years' pains in thumbs, knees, back, feet	Crepitus in knees, tender thickening of lateral meta-tarso-phalangeal joints	Osteoarthrosis
14	F 62	1/128	None	—	,,	Hands, feet	None	Heberden's nodes, hallux rigidus, cervical spine limited	,,

and radiological signs of rheumatoid arthritis was in fact noted amongst the 94 relatives of propositi with a positive S.C.A.T. studied by Lawrence. There is also the possibility that the characteristic of which a positive S.C.A.T. may be an index may predispose the individual to other and as yet undefined disease, and further investigation of this possibility is urgently required.

Population Studies: Screened Samples

Sera from population samples characterized by certain clinical and/or radiological characteristics have also been investigated. These sera were collected by the staff of the Medical Research Council's Pneumoconiosis Research Unit in the course of epidemiological studies.

The first of these concerned an investigation of Caplan's syndrome (Miall *et al.*, 1953) in which a positive S.C.A.T. and/or radiological signs of rheumatoid arthritis in films of the hands and feet were used as diagnostic criteria for confirming the diagnosis of rheumatoid arthritis.

As a result of further studies of Caplan's syndrome (Ball, 1955) and our experience with several cases of obscure lung disease we incline to the view that certain lung lesions may be associated with a positive S.C.A.T. —another possibility that requires further investigation. Miall (1955) and Miall *et al.* (1958) have also studied the general population of the Rhondda Fach, which is a mining valley, and the Vale of Glamorgan, which is a neighbouring agricultural district in South Wales. The whole population was screened for clinical rheumatoid arthritis, using the classical definition of inflammatory polyarthritis of the peripheral joints. In the Rhondda only those individuals who on clinical grounds were considered to have definite or probable rheumatoid arthritis were further investigated radiologically and serologically, but in the Vale even the most doubtful cases were investigated. The S.C.A.T. results in these samples are included in Table X, which is mainly designed to illustrate the effect of the level of clinical diagnosis upon the proportion of positive results in the S.C.A.T. Possible geographic differences in prevalence between Lancashire and South Wales and between urban and rural populations are under investigation, but they are unlikely to invalidate the main findings, which are that the proportion of positive results obtained in any sample of individuals stated to be suffering from rheumatoid arthritis is largely determined by the diagnostic criteria used and the severity of the disease.

The proportion of positive tests in the Rhondda sample and in our own predominantly out-patient material for 1949–50 is very similar, and shows a striking sex difference which is less apparent in hospital in-patients and is altogether absent in the random population sample. At this level of diagnosis and severity there are therefore many women with peripheral polyarthritis which resembles rheumatoid arthritis clinically but which is not associated with a positive S.C.A.T. The nature of this form of polyarthritis is still obscure, but Table XI shows the relationship

TABLE XI.—*S.C.A.T. Results in Relation to Radiological Generalized Osteoarthrosis in Rhondda Females Clinically Graded as Probable or Definite Rheumatoids*

S.C.A.T. Result and Titre	Total No.	With Radiological Generalized Osteoarthrosis			
		Minimal to Severe		Moderate to Severe	
		No.	%	No.	%
Positive 1: 256 and higher	14	0	0	0	0
,, 1: 32 to 1:128 ..	24	11	46	5	21
Negative 1. <4 to 1:16	93	51	55	24	26
Total	131	62	47	29	22

between the S.C.A.T. and radiological gradings of generalized osteoarthrosis in the hand films of the females from the Rhondda who on clinical examination were considered to be suffering from probable or definite rheumatoid arthritis. Of the 38 women with positive tests who were *x*-rayed, only 11 (29%) had definite osteoarthrosis, whereas of the 93 with negative tests 51 (55%) had definite radiological signs of osteoarthrosis. Thus this condition may account for a substantial proportion of peripheral joint disease in middle-aged women which may be classed as possibly rheumatoid in nature as a result of the type of clinical examination that can be carried out in a field survey or in a busy out-patient clinic; our experience of hospital practice since 1952 is in agreement with this, since most of the patients with generalized osteoarthrosis we see in hospital are referred to us as cases of rheumatoid arthritis. This question is discussed more fully elsewhere (Miall *et al.*, 1958).

There may also be other forms of inflammatory polyarthritis in women which have not as yet been characterized. In this connexion it is interesting to note that certain forms of polyarthritis associated with negative tests such as spondylitis and Reiter's disease are at present almost exclusively recognized in males, and it may be that these conditions do in fact also affect females, but in a form which we are at present unable to distinguish on clinical grounds from rheumatoid arthritis.

Conclusions

What can be learned about the clinical significance of the S.C.A.T. from the data presented in this paper?

From the population studies it would appear that the serum factor responsible for agglutination in this system exists in some 5% of the adult urban population in Lancashire, the proportion of positive tests being somewhat higher in old age and somewhat lower in the younger age groups. In this population positive results

TABLE X.—*S.C.A.T. Results at Different Levels of Clinical Diagnosis*

Source	Level of Diagnosis	Males					Females				
		Sample No.	Tested No.	Positive			Sample No.	Tested No.	Positive		
				No.	% of Tested	% of Sample			No.	% of Tested	% of Sample
Leigh survey	Random sample	681	573	31	5	5	758	592	35	6	5
Vale of Glamorgan survey	Screened for polyarthritis, including very doubtful cases	2,279	60	6	10	3	2,342	117	12	10	5
Rhondda survey	Screened for polyarthritis; only definite and probable cases ..	9,430	89	54	61	6	10,292	136	41	31	4
Hospital out-patients	Definite and probable cases ..	—	178	114	64	—	—	464	213	46	—
,, in-patients	Only definite cases	—	149	135	90	—	—	244	205	84	—
,, ,,	,, cases with nodules	—	62	62	100	—	—	91	82	92	—

in the S.C.A.T. show a significant degree of familial aggregation, being found in some 20% of blood relatives of propositi with positive tests. The presence of a positive S.C.A.T. may therefore be genetically determined. If this is so, it may represent an index of some inherited metabolic defect which predisposes the individual concerned to develop certain pathological lesions which from this point of view should be described as features of rheumatoid disease.

It is, however, likely that the disease process itself contributes to the amount of rheumatoid factor found in the serum at any given time. Environmental factors precipitating disease activity are probably important and might even on occasion produce articular disease and a positive S.C.A.T. in patients not genetically predisposed, so that the problem may be very complicated and much more work is required before the whole story can be unravelled. Nevertheless the idea of an inherited predisposing metabolic defect provides a most useful working hypothesis for the purpose of further studies.

From the study of patients in hospital it is clear that a positive S.C.A.T. is very closely associated with the rheumatoid necrobiotic nodule and a certain type of erosive polyarthritis of the limb joints and upper spine. On the other hand, there are clearly many forms of erosive polyarthritis which are not associated with a positive S.C.A.T., and these we would by definition exclude from our concept of rheumatoid disease.

High titres in the S.C.A.T. may also be associated with certain vascular lesions which may occur independently or as a part of diffuse connective-tissue diseases such as systemic lupus erythematosus and systemic sclerosis. These conditions are, however, relatively uncommon, and their relationship to the rheumatoid serum factor and the more common articular and nodular manifestations of rheumatoid disease requires further investigation. There may also be other as yet undefined lesions which might be brought to light by a study of individuals with a positive S.C.A.T. and/or their relatives.

The study of rheumatic diseases has been severely hampered by the lack of precise definition and aetiological classification. Certain notable advances were made in the past, such as the distinction between inflammatory and degenerative joint disease, the definition of gout in terms of hyperuricaemia and an inherited or acquired disorder of uric acid metabolism, and the demonstration of the role of streptococcal infection in rheumatic fever. Perhaps a definition of rheumatoid disease in terms of the rheumatoid serum factor may prove equally valuable.

Summary

Since 1949 the rheumatoid serum factor has been estimated by the same technique using a sensitized sheep cell agglutinating system (S.C.A.T.). This test has been done routinely on sera from all patients admitted to the rheumatism beds of the Manchester Royal Infirmary and from selected groups of out-patients. The test has also been carried out on sera collected during surveys of both random and screened samples of the general population.

A positive result in the S.C.A.T. was found in 93% of 382 in-patients with rheumatoid arthritis in whom great care was taken to establish the correctness of the diagnosis. Of these patients 152 had subcutaneous nodules, and 98% of these cases had positive tests. Positive tests were obtained in 70% of 64 patients with rheumatoid arthritis of less than one year's duration and in 68% of 41 patients with rheumatoid arthritis in whom an alternative diagnosis was recorded at some stage of their care in hospital. In both these groups the diagnosis was less certain, and this is reflected in the lower proportion of positive tests.

Some 40% of positive tests were found in patients with systemic lupus erythematosus, with systemic sclerosis, and also in patients with a form of endarteropathy affecting digital or pulmonary vessels; but the S.C.A.T. was usually negative in other forms of arterial disease and in dermatomyositis.

A positive S.C.A.T. was found in only 6.7% of sera from 1,392 patients attending hospital for other forms of arthritis, though many of these patients, such as those with atypical spondylitis, Reiter's disease, and psoriatic arthropathy, had severe inflammatory erosive polyarthritis which resembled rheumatoid arthritis in many respects.

A positive S.C.A.T. was found in 5.7% of 1,165 sera from a random sample of the adult population of a Lancashire town. In this population positive tests were fairly evenly distributed between the sexes and throughout the age groups tested although the proportion of positive tests was somewhat higher in the older and lower in the younger subjects. Positive tests showed a substantial degree of familial aggregation, being found in 20% of 94 blood relatives of propositi with positive tests.

These findings are discussed, and it is concluded that the rheumatoid serum factor may represent an index of some inherited metabolic characteristic which predisposes the individual to rheumatoid arthritis and certain other forms of disease that may not yet be fully defined. Conversely many other forms of inflammatory erosive polyarthritis appear to be unrelated to this characteristic.

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TOTAL THORACIC SUPERVOLTAGE IRRADIATION FOLLOWED BY THE INTRAVENOUS INFUSION OF STORED AUTOGENOUS MARROW

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The inevitable result of large-volume high-dosage radiotherapy is damage to bone marrow and a subsequent lowering of the circulating blood elements. This factor, combined with the adverse constitutional effects on the patient, has undoubtedly prevented the full exploitation of radiation in the disseminated radiosensitive tumours.

Many workers have described the severe and sometimes permanently damaging effects to marrow that can follow from a dosage of radiation well below that used by the radiotherapist in the treatment of cancer. Stewart (1958), in a study of 126 patients with ankylosing spondylitis, comments that 2,000 r may render the bone marrow hypoplastic for years and that after 4,000 r there is no recovery in 50% even after several years. This substantiates the observation of Humble (1948), who has shown the profound effect on cellularity which can accrue from moderate dosage radiotherapy (Table I).

Kurnick *et al.* (1958) described the use of stored autogenous marrow to combat the haemopoietic depression which followed multiportal techniques when giving 400 kV *x*-ray therapy to approximately 2,000 r tissue dose over a total period of two months in a patient with a disseminated testicular tumour. They were able on two quite distinct occasions to restore to more normal limits severely depressed peripheral blood-cell counts. A further patient with renal carcinoma was given 700 r centre dose to the torso in 10 days, presumably at the same kilovoltage as the first patient. Here no benefit followed the bone-marrow infusion. Both their patients died—the first four months after the initial marrow infusion, and the second 10 days after the injection of bone marrow. This valuable work demonstrated clearly the ability of the body to reaccept stored autogenous marrow even though the therapeutic effect of the radiation was disappointing.

TABLE I.—*Effect of Direct X-irradiation on Sternal Marrow After 2,000 r in 22 Days*

	Before Irradiation	After Irradiation
Total nucleated count	56,000 per c.mm.	9,200 per c.mm.
Myeloblasts	0·4%	0·0%
Promyelocytes	1·8%	0·0%
Myelocytes, neutrophil	11·2%	0·2%
Metamyelocytes ,,	0·0%	0·2%
Polymorphs, ,,	41·0%	72·4%
Myelocytes, eosinophil	2·4%	0·0%
Polymorphs, ,,	1·8%	0·6%
Myelocytes, basophil	0·2%	0·0%
Polymorphs, ,,	0·0%	1·2%
Proerythroblasts	0·2%	0·0%
Normoblasts, early	3·6%	0·0%
,, intermediate	11·0%	0·0%
,, late	3·4%	0·0%
Lymphocytes	19·6%	12·4%
Monocytes	2·8%	12·4%
Plasma cells	0·4%	0·6%
Reticulum cells	0·0%	0·0%
Macrophages	0·0%	0·0%
Megakaryocytes	0·2%	0·0%
Myeloid/erythroblast ratio	3·23:1	—

Note the almost complete aplasia of the second specimen.

It was decided to treat the entire thorax of selected patients with multiple pulmonary metastases by means of the 2 MeV Van de Graaff generator. This apparatus has certain advantages, as described below, when compared with more conventional machines. It was anticipated that the treatment of such large volumes of tissue, apart from the haematological effects, must inevitably result in considerable constitutional disturbance with much nausea, vomiting, and distress. Therefore it was decided to shorten the overall treatment time in an attempt to obtain a uniform dose of 3,000 r in two weeks. This programme has now been carried out in two cases. Somewhat to our surprise, it was found that one (Case 2) of the two patients tolerated this course of treatment with virtually no constitutional disturbance whatsoever. This does not, of course, refer to the haematological response which is mentioned in the description of the individual cases.

Case 1

A woman aged 22 was referred to Sir Stanford Cade on February 13, 1957, with pain in the right wrist of three or four weeks' duration. She was found to have a highly vascular bone lesion at the lower end of the right ulna, which on clinical and radiographic grounds was thought to be an osteogenic sarcoma. In view of the vascularity, biopsy was not done. Treatment was given by means of 2 MeV *x* rays from February 19 to April 15 to a maximum tumour dose of 7,000 r. This resulted in complete relief of pain and marked recalcification of the tumour. The patient remained well until she attended the hospital on September 10, 1958, complaining of dyspnoea and loss of

2 stone (12.7 kg.) in weight. Radiographs of the chest at this time showed the presence of multiple metastases in the left lung, with the appearance of a large effusion on the right side with a considerable deposit above it. The right ulna itself remained entirely symptomless and good recalcification was seen to have taken place.

On September 22 a light general anaesthetic was given and marrow was aspirated from both iliac crests and the sternum, approximately 1.1×10^8 cells being obtained. This was frozen and stored at $-79°$ C. as described below.

On September 23 treatment to the entire thorax was begun.

Details of Radiotherapy

September 23 to October 7, 1958. Period of treatment, 2 weeks: 2 MeV *x* rays. F.S.D. 122 cm. Two opposing fields, each 25×30 cm. approx.

First five days with 2 MeV *x* rays	Skin dose	=	1,199 r
	Maximum tumour dose	=	1,102 r
	Minimum tumour dose	=	946 r
Next four days with 2 MeV *x* rays	Skin dose	=	2,399 r
	Maximum tumour dose	=	2,202 r
	Minimum tumour dose	=	1,890 r

Picker *x*-ray set 250 kV *x* rays. H.V.L. 3.4 mm. Cu. F.S.D. 75 cm. Two opposing fields, each 25×30 cm.

Final 2 days 250 kV *x* rays	Skin dose	=	2,999 r	Final total dose in röntgens
	Maximum tumour dose	=	2,708 r	
	Minimum tumour dose	=	2,250 r	

These are equivalent to absorbed doses:

Total skin dose	=	2,920 rads
Maximum total soft tissue dose	=	2,637 rads; maximum total "average bone dose"=2,533 rads
Minimum total soft tissue dose	=	2,191 rads; minimum total "average bone dose"=2,083 rads
Estimated integral dose	=	39.4 megagram-röntgens.

Five days after the start of *x*-ray therapy the patient complained of generalized pain in the chest, both anteriorly and posteriorly, characterized by tenderness of the ribs and sternum and accompanied by rise in temperature and pulse rate. Within three days the pain had gone, but it returned on the day of completing treatment. On this occasion she was obviously distressed and unwell, and by the next day was cyanosed. On October 9 her stored marrow was thawed and infused intravenously, the whole procedure taking one and a half hours. Over the next two days the general condition improved markedly and she was discharged from hospital on October 22. Two days before, during, and after the *x*-ray therapy the following medicaments were prescribed daily: prednisone 20 mg. and vitamin K 100 mg. daily, and perphenazine 4 mg. t.d.s.

Haematological Findings.—Fig. 1 shows that after the marrow infusion there was an immediate rise in the total circulating white cells. This rise is not readily accounted for on a basis of marrow repopulation, nor was it merely due to cessation of *x*-ray therapy. The most readily acceptable explanation lies in postulating a non-cellular humoral factor in the marrow injection which has the property of almost immediately stimulating haematopoiesis in the bone marrow undamaged by irradiation. This is borne out by the observation of Kurnick *et al.* (1958), who demonstrated by means of serial marrow punctures that haematopoietic foci only became evident two weeks after the infusion of marrow.

It is well seen in Table II that there is considerable evidence of marrow regeneration 13 days after the marrow infusion.

Progress.—The patient, on completion of treatment on October 7, soon began to feel much better, so much so that by October 22 she insisted on returning to her home in Ireland and was not seen at the Westminster Hospital until November 19, when she complained of a severe dry cough. By December 10 this cough began to be accompanied by dyspnoea, which became progressive and necessitated her readmission on December 15. The respiratory distress became more severe with persistent cyanosis. The patient became progressively weaker and died on December 23. Radiographs of the chest had shown no regression of the metastatic malignant disease nor indeed any progression. Permission for a post-mortem examination was not obtained.

TABLE II.—*Bone-marrow Differentials in Case 1*

	Before Irradiation	14 Days after Completing Irradiation	8 Weeks after Completing Irradiation
Date	16/9/58	21/10/58	5/12/58
Total nucleated count	50,000 c.mm.	22,000 c.mm.	41,000/c.mm.
Myeloblasts	1·6%	0·0%	0·6%
Promyelocytes	1·6%	0·2%	2·4%
Myelocytes, neutrophil	9·4%	2·4%	13·2%
Metamyelocytes, ,,	7·8%	1·6%	8·4%
Polymorphs, ,,	34·2%	52·4%	47·6%
Myelocytes, eosinophil	0·6%	0·0%	0·2%
Polymorphs, ,,	2·4%	0·4%	0·8%
Myelocytes, basophil	0·0%	0·0%	0·0%
Polymorphs, ,,	0·0%	0·2%	0·2%
Proerythroblasts	0·2%	0·4%	0·4%
Normoblasts, early	9·6%	11·0%	7·8%
,, intermediate	6·2%	7·2%	5·2%
,, late	0·0%	0·0%	0·0%
Lymphocytes	16·6%	8·8%	5·0%
Monocytes	8·2%	11·4%	7·4%
Plasma cells	0·4%	1·0%	0·4%
Reticulum cells	0·8%	1·4%	0·0%
Macrophages	0·4%	1·6%	0·2%
Megakaryocytes	0·0%	0·0%	0·2%
Myeloid/erythroblast ratio	3·6: 1	3·07: 1	5·65: 1

Case 2

A young woman aged 21 was referred to Sir Stanford Cade on October 20, 1956, and treated by 2 MeV *x* rays to 5,500 r for a Ewing's tumour of the left ischium. Following this treatment she remained well until July 2, 1958, when a routine radiograph of the chest revealed multiple small bilateral pulmonary metastases. In spite of the administration of chlorambucil ("leukeran"), 7 mg.

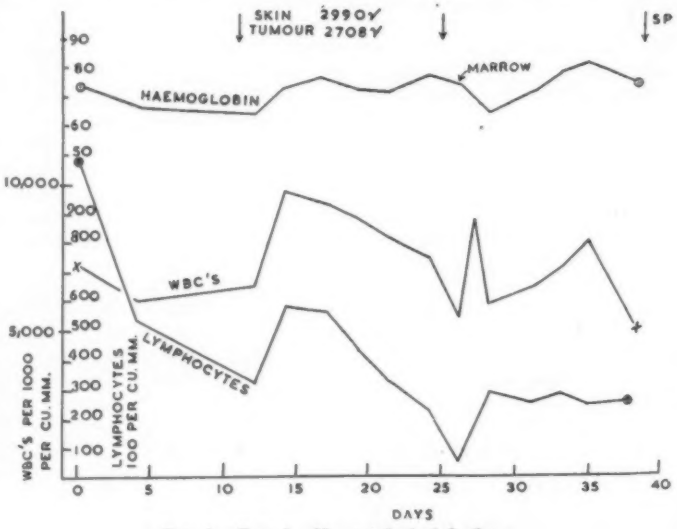

FIG. 1.—Case 1. Haematological findings.

daily, these metastases steadily increased in size. It was therefore decided to treat the entire thorax contents as in the previous patient.

On October 23 marrow was aspirated under general anaesthesia from the right iliac crest spines of the lumbar vertebrae and sternum, a total of approximately 0.75×10^9 cells being obtained. The marrow was then frozen and stored.

On October 24 treatment to the entire thorax was started.

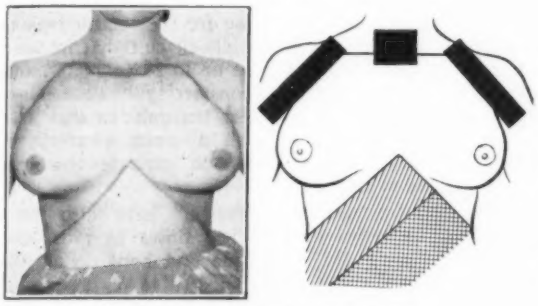

FIG. 2.—Method of delineating the field.

Details of Radiotherapy

October 24 to November 7, 1958. Period of treatment, 2 weeks. All with 2 MeV *x* rays. F.S.D. 122 cm. Two opposing fields, each 26×31 cm. approx.

Total skin dose	=	3,100 r
Total maximum tumour dose	=	2,933 r
Total minimum tumour dose	=	2,518 r

These are equivalent to absorbed doses:

Total skin dose	=	3,023 rads
Maximum total soft tissue dose	=	2,860 rads; maximum total "average bone dose"=2,552 rads
Minimum total soft tissue dose	=	2,455 rads; minimum total "average bone dose"=2,191 rads
Estimated integral dose	=	45.3 megagram-röntgens.

As in the previous patient, prednisone 20 mg., vitamin K 100 mg. daily, and perphenazine 4 mg. t.d.s. were prescribed as before, during and after treatment.

The method of delineating the field by means of lead blocks is shown in Fig. 2.

Throughout the two-weeks course of treatment this patient insisted that she felt well in every way and ate with good appetite. On November 7 the marrow was thawed and reinjected intravenously as described below, the whole procedure taking one and a half hours and being quite free of untoward effects.

The effect on the pulmonary metastases was rapid (Fig. 3).

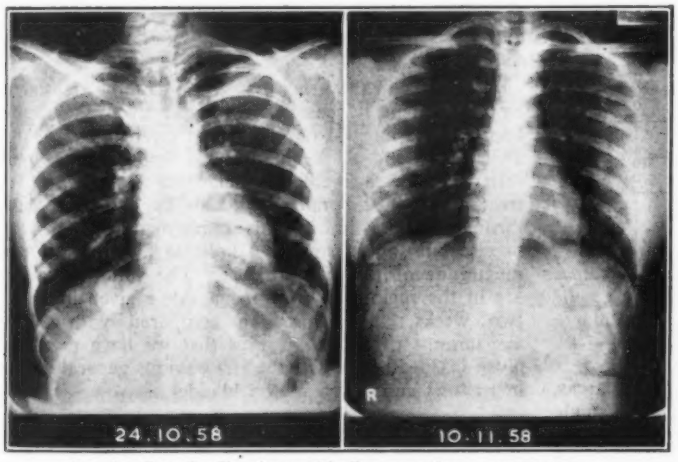

FIG. 3.—Case 2. Showing rapid effect on pulmonary metastases.

Haematological Findings.—Fig. 4 shows a rapid rise in the total white-cell count following the injection of marrow.

The sequence of events is represented diagrammatically in Fig. 5.

Table III demonstrates one month after the marrow infusion that regeneration is taking place.

At the time of writing this patient was well; her only complaint was a dry cough, but the chest radiographs remained entirely clear of any suspicion of recurrent malignant disease.

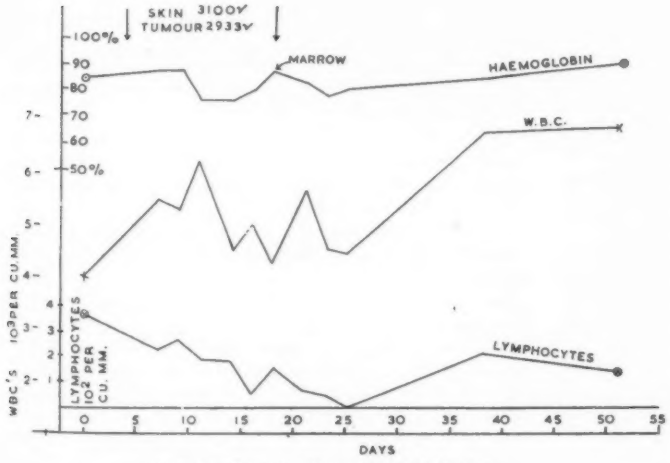

FIG. 4.—Case 2. Haematological findings.

Physical Aspects of the Radiotherapy

Two-million-volt *x* rays (H.V.L. 7.4 mm. Pb) from a Van de Graaff electrostatic generator (Wilson and Perry, 1952) were chosen for treating these patients for a number of reasons. The apparatus provides large fields of penetrating radiation such that by means of an opposing field-treatment technique it is possible to obtain fairly good dosage homogeneity throughout thick masses of tissue. It also provides dose rates great enough to enable treatments to occupy a reasonable time even at quite large F.S.D.s. The differential *x*-ray absorption in bone and soft tissue is relatively small, so that differences between the energy absorbed in bone and soft tissue are minimal.

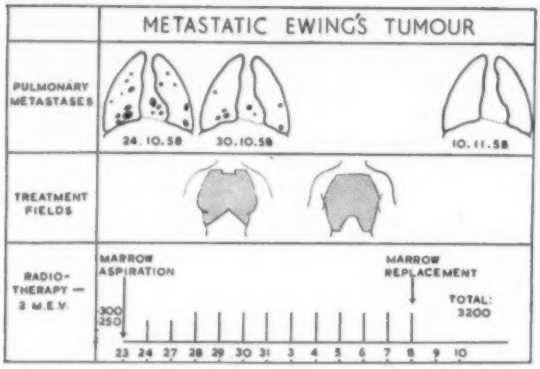

FIG. 5.—Case 2. Sequence of events.

TABLE III.—*Bone-marrow Differentials in Case 2*

	Prior to Irradiation	1 Month after Marrow Infusion
Date	21/10/58	10/12/58
Total nucleated count	130,000/c.mm.	31,000/c.mm.
Myeloblasts	2·2%	0·2%
Promyelocytes	6·4%	1·2%
Myelocytes, neutrophil	22·8%	23·0%
Metamyelocytes, ,, ...	8·4%	7·8%
Polymorphs, ,, ...	20·6%	31·2%
Myelocytes, eosinophil	2·8%	0·4%
Polymorphs, ,, ...	3·8%	0·2%
Myelocytes, basophil	0·0%	0·2%
Polymorphs, ,, ...	0·2%	0·6%
Proerythroblasts	0·4%	1·4%
Normoblasts, early	10·6%	8·2%
,, intermediate ..	8·0%	10·4%
,, late	0·0%	0·0%
Lymphocytes	8·0%	5·8%
Monocytes	4·0%	7·0%
Plasma cells	0·6%	1·2%
Reticulum cells	0·2%	1·2%
Macrophages	0·4%	0·0%
Megakaryocytes	0·6%	0·0%
Myeloid/erythroblast ratio ..	2·1: 1	3·57: 1

The treatments necessitated irradiation of large areas, and in order to do this with the least ambiguity a single field to cover the whole area is normally preferred. Therefore, in order to obtain a sufficiently large field area, it was usually necessary to treat at an F.S.D. of more than 100 cm. Our standard depth-dose data for this radiation (Wilson and Perry, 1952) were measured for 100 cm. F.S.D., so that it was necessary to extrapolate these in order to assess the depth doses for the conditions used. In practice the fields used were not regular geometrical shapes. They were shaped so as to delineate the boundaries of the lung fields and afford protection so far as was possible to adjacent structures by means of lead bricks 1½ in. (3.8 cm.) thick (permitting only about 3% transmission), which were simply and easily mounted on a platform attached to the machine and situated between the patient and the adjustable diaphragm. To facilitate this the patients were treated lying down with the beam directed vertically downwards. The treatment comprised anterior and posterior fields, both being applied at each treatment session.

The dose values quoted previously for individual patients are all based on water phantom measurements. The skin dose is the dose 4 mm. beneath the skin surface where electronic equilibrium is established. The maximum tumour dose is the greatest dose estimated to have been received by the tumour-bearing area, and the minimum tumour dose is the smallest dose estimated to have been received by the same area. In deriving the latter the fall in dose towards the edge of a beam has been taken into account. The three dose values taken together indicate the degree of dose homogeneity that was obtained throughout the treated volume. In fact, of course, because chiefly lung tissue is irradiated, the true dose values may be somewhat different from those calculated in this way. The work of Burlin (1957) with cobalt-60 gamma rays shows that the true values will be greater, and this is especially so for the central regions of the treated tissue. His results suggest that in these regions the actual dose may be up to 20% greater, and this should be borne in mind considering the dose values quoted previously. The greater transmission that lung tissue has as compared with a water phantom is advantageous in that it helps to increase the dose homogeneity in the treated tissue.

The incident doses in röntgens have also been expressed in terms of absorbed doses in rads, and values are given for soft tissue and bone. For soft tissue one röntgen has been equated to 0.975 rad for 2 MeV *x* rays and 0.968 rad for 250 kV *x* rays. For bone it is more difficult to be definite, so that values have been assumed which correspond to average for bone as interpreted by Spiers (1951). These are 0.870 rad per röntgen for 2 MeV *x* rays and 1.22 rads per röntgen for 250 kV *x* rays.

In relation to the general toleration of the treatment by the patient it seemed of interest to evaluate the approximate integral dose that was given in each case. This was done by evaluating the approximate total volume of tissue irradiated (field area × thickness of treated tissue) and multiplying this by the mean dose throughout the volume. This simple method is not very precise but should suffice to indicate the approximate magnitude of the integral dose. The values obtained are in the region of 40–50 megagram-r given in about two weeks. This may be compared with 20–30 megagram-r of 2 MeV *x* rays that we have regularly given in 35–50 days without any obvious general effects in treating carcinoma of the bladder.

Preparation and Preservation of the Marrow Cell Suspension

Marrow is obtained by aspiration from multiple punctures of the anterior and posterior iliac crests, lumbar vertebral spines, and sternum (Humble and Newton, 1958) under a general anaesthetic. Normally 30–60 ml. of marrow is aspirated in this manner, yielding a total of $0.5–1.5 \times 10^9$ nucleated cells.

The aspirated marrow is delivered under strictly aseptic conditions into McCartney bottles containing 10 ml. of a cell suspension medium composed of Hanks's balanced salt solution (Hanks and Wallace, 1949) with 10% inactivated human AB serum, 0.1% Bacto yeast extract (" difco "), 0.25% glucose, penicillin (100 u./ml.), streptomycin (0.1 mg./ml.), and heparin (2.5 mg./ml.). The suspension is then sieved by a modification of Thomas's (1955) method. In our technique the suspension is passed 20 times through a coarse stainless-steel mesh (40 strands per inch) followed by 10 passages through a finer mesh (200 strands per inch). A micro-filter syringe supplied by R. B. Turner and Co. is used for this purpose, steel mesh supplied by Messrs. Johnson Matthey being inserted between the rubber washer and the perforated screen at the end of the

syringe. The marrow suspension is now centrifuged at 200 *g* for 20 minutes. The fat and supernatant fluid are aspirated using a 17-gauge blunt needle attached to a filter pump, as it is possible by this method to remove the entire disk of fat in one piece.

The sedimented cells are resuspended in 10 ml. of the cell-suspension medium and transferred through the fine stainless-steel mesh into an equal volume of cell-suspension medium containing 30% "analar" glycerol, a small portion being retained for a nucleated cell count. Thus the final glycerol concentration is 15% v/v. After equilibration for 10 minutes the suspension is sealed in 7-ml. aliquots in glass ampoules, and cooled at 1° C. per minute to −15° C. and thereafter at a rate not exceeding 10° C. per minute to −79° C. as described by Barnes and Loutit (1955). Originally we attempted to use the apparatus of Polge and Lovelock (1952), but, like Barnes and Loutit (1955), we found that our model failed to produce the desired characteristics, and we have now developed a simple apparatus capable of producing automatically a wide range of two-stage cooling curves. Details of this apparatus will be published elsewhere. The frozen marrow is stored in Dewar flasks containing methylated spirit and solid carbon dioxide, the flasks themselves being kept in an insulated cabinet packed with solid carbon dioxide (Polge and Lovelock, 1952).

When required, the marrow cells are reconstituted by the method of Sloviter (1956) as modified by Ferrebee *et al.* (1957). In this procedure, which is designed to reduce the osmotic trauma to the cells, the ampoules are rapidly thawed in a water-bath at 38° C. and immediately added to 3.5 ml. of Hanks's balanced salt solution (Hanks and Wallace, 1949) to which has been added 35 g. of glucose per 100 ml. After two minutes 7 ml. of the basic cell suspension without heparin is added, and mixed well. This is repeated after a further two minutes. We have found the marrow reconstituted in this manner to be rather unstable, and we therefore administer it within five minutes of the final dilution.

Discussion

Large-volume high dosage radiotherapy is justified in the treatment of cancer should it be thought possible to eradicate even though temporarily disseminated disease. That it is possible to destroy permanently metastatic disease in a radiosensitive tumour at a dose level in the order of 3,000 r is clearly shown by Prossor (1959), who gives a 10-year survival figure of 15% in those patients who presented with glandular metastases from testicular tumours.

It would seem at first sight that the use of stored autogenous marrow is contraindicated should a diagnostic marrow puncture reveal the presence of malignant cells. This may certainly be true, but it is worth pointing out that the marrow is reinfused intravenously, and it is accepted that the percentage of circulating malignant cells in the blood which actually form metastases is extremely small (Roberts *et al.*, 1958).

The whole premise for the use of stored autogenous marrow is the known damage which results following the application of radiation to large areas of marrow-containing spaces. The ability of the body to accept autologous grafts is well known, and there is good evidence that this applies to bone marrow itself (Kurnick *et al.*, 1958).

It is desirable that irradiation to large volumes should be accomplished with minimal upset to the patient. That this is possible is shown by our second patient, who experienced no immediate untoward side-effects whatsoever directly attributable to the irradiation.

The severe dyspnoea and respiratory symptoms which followed the radiotherapy to the first patient may possibly have been due to progress of the metastatic disease and/or diffuse parenchymatous pulmonary fibrosis. It was not possible to obtain permission for a post-mortem examination.

Possible Future Applications

(1) The immediate prospect is an extension of the treatment volumes. There would seem to be no good reason why considerably larger volumes should not be treated. It is recognized that individual organs—for example, the kidney (Paterson, 1952)—are unable to withstand homogeneous irradiation in excess of 2,000 r in five weeks or less. Nevertheless it is possible to shield such organs and lessen the given irradiation dose.

(2) It is now clear that the entire thorax can be irradiated to 3,000 r in two weeks with no constitutional disturbance.

(3) The more widespread the metastatic disease the greater would be the indication for chemotherapy. In the later stages of the radio-sensitive tumours it is not uncommon for the patient to develop widespread cutaneous and other metastases. Technically it is difficult to give total body irradiation, and in these cases a reasonable alternative would be the use of massive chemotherapy provided that stored autogenous marrow is used to restore the cellularity of the bone marrow itself. This massive quick chemotherapy has already been done with marrow replacement, and will be the subject of a separate report.

Summary

Total thoracic supervoltage radiation to 3,000 r tissue dose in two weeks has been given to two patients with metastatic pulmonary disease. An attempt has been made to combat the haematological depression by the used of stored autogenous marrow.

We gratefully acknowledge the constant encouragement and interest shown by Sir Stanford Cade in this work and his ready permission to use his cases. We also acknowledge our indebtedness to Dr. Sidney Farber, of the Children's Hospital, Boston, U.S.A., for the method of charting Case 2. We thank Miss P. Wheatley and Miss B. Hedley-Prole for their help in the preparation of the manuscript, and Dr. Peter Hansell for the photographic illustrations.

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REGRESSION OF AMYLOIDOSIS SECONDARY TO RHEUMATOID ARTHRITIS

BY

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The steady decrease in uncontrolled sepsis and tuberculosis in the last few decades has revealed rheumatoid arthritis to be important as a cause of amyloidosis. Extensive renal damage may result from the deposition of amyloid material in the renal arterioles and glomerular basement membrane. These changes often lead to proteinuria and the development of the nephrotic syndrome, while progressive renal failure and death in uraemia is a common termination (Abrami *et al.*, 1931; Rosenblatt, 1933; Gedda, 1955). Trasoff *et al.* (1944) noted a 91% mortality in recorded rheumatoid cases. We have seen uraemic death in four out of eight patients at Hammersmith Hospital (Missen and Taylor, 1956).

Recovery from secondary amyloidosis due to tuberculosis (Waldenström, 1928; Rosenblatt, 1936) or sepsis (Walker, 1928; Sherlock, 1945) has occasionally been described, but only two cases have been recorded with apparent recovery from amyloidosis secondary to rheumatoid arthritis. Trasoff *et al.* (1944) reported the development of heavy proteinuria, hypoproteinaemia, and gross anasarca in a 14-year-old girl with a three-year history of severe juvenile rheumatoid arthritis. Amyloidosis was suspected, and a 70% tissue retention of Congo red supported the diagnosis, although no histological proof was obtained. Treatment with liver extract and transfusions of plasma was accompanied by decrease in the activity of the arthritis and disappearance of the nephrotic syndrome. Five years later the arthritis was inactive and no evidence of amyloid disease was detected. The tissue retention of Congo red had fallen to 15%. The clinical course and changing Congo-red tests suggested the development and resolution of amyloidosis in this patient.

The case described by Kennedy (1935) followed a similar course, but again no histological studies were made and the follow-up was short. This 43-year-old man developed proteinuria and anasarca 18 months after the onset of severe generalized arthritis. The initial Congo-red test showed only 37% tissue retention, but this rose to 74% two months after the onset of proteinuria. Improvement occurred following treatment with an oral liver preparation, and six months later oedema was absent and proteinuria reduced to a trace. The Congo-red tissue retention had fallen to 27%, but no further follow-up was recorded.

These reports suggest that complete and prolonged control of rheumatoid activity might allow regression of secondary amyloidosis. The introduction of corticotrophin and steroid hormones raised the hope that adequate control of rheumatoid disease would become possible. Suppression of the clinical signs of rheumatoid activity is difficult to achieve with steroids, and the high maintenance dose required often results in the development of troublesome effects. These hormones, however, produce considerable symptomatic benefit in patients with the nephrotic syndrome by abolishing proteinuria and oedema. On theoretical grounds at least these hormones might be expected to have a beneficial effect on amyloidosis secondary to rheumatoid arthritis, particularly in those patients developing the nephrotic syndrome.

Clinical evidence of the effect of corticotrophin and steroids on amyloidosis is conflicting and generally unfavourable. McCall and Fisher (1953) described improvement in two out of three patients with primary laryngeal amyloidosis treated with corticotrophin and cortisone respectively. Shuttleworth and Ross (1956) observed no increase in the incidence of amyloidosis in steroid-treated lepromatous leprosy, a disease frequently complicated by amyloidosis. They noted that these hormones did not influence established amyloid disease. However, West and Newns (1952) reported the case of a patient with rheumatoid arthritis with a normal liver biopsy prior to cortisone treatment, who after initial improvement on cortisone deteriorated, death occurring one year later. Amyloidosis was found at necropsy. Cortisone had failed to produce any favourable effect on the course of the disease in this case, and could have aggravated its development. Paulsen (1950), Bjørneboe *et al.* (1952), Schneckloth and Page (1955), and Goodman and Baxter (1957) report a total of seven cases of amyloid nephrosis treated with steroids. The amyloidosis was thought to be primary in four and secondary in three. The response was uniformly poor, and in Paulsen's two patients the proteinuria was increased.

Experimental evidence is conflicting. A number of workers have studied the influence of steroid hormones and corticotrophin on experimental amyloidosis produced in mice and rabbits by the injection of sodium caseinate. Grayzel *et al.* (1956) demonstrated a protective action of corticotrophin and cortisone in certain doses, while Latvalahti (1953) and Peräsalo and Latvalahti (1954) showed that these hormones increased the incidence of amyloidosis in treated animals.

There is also some clinical and experimental evidence suggesting an association between thyroid lack and amyloidosis. Myxoedema may be complicated by the development of amyloidosis, and Symmers (1956) mentions three such cases, one of which showed clinical recovery from the amyloidosis when treated with thyroid hormone. Experimental thyroidectomy increases the incidence of amyloidosis in mice injected with sodium caseinate, while thyroid hormone reverses this effect (Peräsalo and Latvalahti, 1954). While it is difficult to draw conclusions from experimental amyloidosis, these facts suggest that thyroid hormone may be of importance in protecting tissues from the deposition of amyloid material and might favour reabsorption.

The purpose of this paper is to describe the progress of two patients with rheumatoid arthritis complicated by amyloidosis in whom remissions of the rheumatoid disease were followed by apparent regression of the amyloidosis. The part played by steroid hormone in the treatment of these and other patients is discussed. Two patients received a course of treatment with triiodothyronine, and the results are described.

Case 1

In July, 1947, a girl, then aged 5 years, was first admitted to the Rheumatism Research Unit of the Canadian Red

Cross Memorial Hospital with severe generalized rheumatoid arthritis of two years' duration. At that time she was severely ill, with widespread active joint involvement, high fever, and a sedimentation rate between 43 and 68 mm./hour. The liver and spleen were not enlarged and no proteinuria was noted on repeated testing with salicyl-sulphonic acid over the next two and a half years. Serum proteins (8.5 g.%) showed an A/G ratio of 2.4. In this period she was gradually remobilized despite persistent disease activity. In June, 1950, an exacerbation of joint symptoms necessitated readmission: the liver edge was noted to be 5 cm. below the costal margin, the spleen was not palpable, and the E.S.R. had risen to between 60 and 120 mm./hour. Proteinuria was detected, about 300 mg./100 ml., and the daily urinary protein excretion was found to vary between 2 and 4 g. Intravenous pyelography showed no abnormality but a Congo-red test (September, 1950) showed 37% tissue retention in one hour, none being excreted in the urine. Gum biopsy was negative for amyloid but liver biopsy showed moderately severe amyloidosis maximal in the mid-zonal region.

On her third admission (July to November, 1951) with active joint disease, the liver had enlarged further and the spleen was now palpable. Proteinuria had increased further (3–5 g./day) and serum protein had decreased (4.6–6.8 g.% with an A/G ratio between 1.1 and 2.3). Cortisone given at 100 mg./day for a six-weeks period temporarily reduced the E.S.R. from its former level of about 100 mm./hour to 50 mm./hour but failed to affect fever, hepatosplenomegaly, or proteinuria: Congo-red tissue retention changed from 70% just before hormone therapy to 95% just after.

During 1952 the disease activity decreased, the E.S.R. fell (50 mm./hour), and the spleen was no longer palpable. Improvement continued during her fourth admission, July, 1953, to September, 1954: the E.S.R. fell from 26 to 10 mm./hour, the liver became smaller, and proteinuria was absent on repeated testing. With this the serum protein rose to a range of 7.5–8.6 g.% with an A/G ratio of 2–2.4. Congo-red tissue retention at one hour was still, however, 92%. In March, 1955, she appeared to be in remission, with spleen and liver impalpable, proteinuria absent, and E.S.R. 10 mm./hour.

A sudden exacerbation with fever occurred necessitating her fifth admission (November, 1955, to March, 1956) with E.S.R. 100 mm./hour, decrease in serum protein (5 g.%), and reappearance of protein in the urine (5–16 g./day). This gradually settled again and protein was absent in August, 1956, and March, 1957. In September, however, traces appeared (15 mg./100 ml.), and in November a renal exacerbation with oedema and massive proteinuria up to 20 g./24 hours led to her sixth admission. This nephrotic phase without rheumatoid activity, without liver or spleen enlargement, but with an E.S.R. of 100 mm./hour has lasted up to the time of writing, with concomitant fall in serum protein. The blood urea has risen to 49 mg./100 ml. with a transient episode of retention up to 160 mg./100 ml.

Comment.—This child suffered from prolonged active rheumatoid arthritis and developed classical amyloid disease, the signs of which regressed completely during a prolonged remission of arthritis, only to return with a further exacerbation of rheumatoid activity. A short course of cortisone given in 1951 did not immediately influence the arthritis or the amyloidosis, and the only observed change during this time was an increase in the tissue retention of Congo red. The remission of the arthritic process appeared to occur spontaneously over the next six months following cortisone therapy. A shorter remission appeared subsequently. The development of the typical nephrotic syndrome in 1957 not associated with increased joint activity indicates that the underlying renal damage is extensive, and that reabsorption of the amyloid deposits did not occur in the period of clinical improvement.

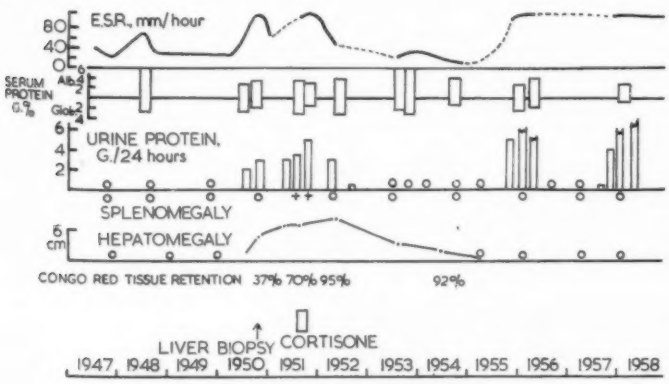


FIG. 1.—Case 1. Course and treatment.

Case 2

In 1948 a man, then aged 24, contracted pulmonary tuberculosis. A right-sided thoracoplasty was performed in 1950, since when the chest disease has remained clinically and radiologically inactive. In 1952 he developed polyarthritis of the rheumatoid type with fever, pain, swelling, and effusion of the small joints of the hands, wrists, elbows, knees, and ankles. No significant hepatosplenomegaly was detected and proteinuria was not found on repeated testing in the ward. The E.S.R. varied between 60 and 100 mm./hour. The Rose–Waaler sheep-cell test was negative, and *x*-ray films of the involved joints and spine showed only osteoporosis. Despite bed rest and treatment with salicylates, local heat, and splints, the disease remained active (see Fig. 2). Phenylbutazone gave some relief until dyspepsia prevented its further use.

TABLE I.—*Treatment with Triiodothyronine*

Case No.		Liver (cm.)	Spleen (cm.)	E.S.R. (mm./hr.)	Urea (mg.)	Urine Protein (g./24 hr.)	Alb./α_2 Ratio
2	Before treatment	13·0	0	132	18	6·6	1·1
	After 30–480 μg. for 8 weeks ..	13·5	0	110	20	8·5	1·4
3	Before treatment	1	0	107	41	7·6	2·1
	After 30–120 μg. for 4 weeks ..	0	0	100	40	3·8	2·5

Proteinuria was detected in May, 1953, and the patient was admitted for further investigation. Examination showed persistent rheumatoid activity in the hands, elbows, and knees. The spleen was not felt, but the liver edge was palpable 2 cm. below the costal margin. Proteinuria varied between 1 and 4 g. a day, the E.S.R. was 50 mm./hour, and blood urea 30 mg./100 ml. A Congo-red test showed 94% tissue retention at one hour. Biopsy of the buccal membrane was normal, but liver biopsy disclosed amyloid deposits.

Treatment with cortisone in doses up to 125 mg. daily failed to control the arthritic symptoms, and during the next ten months hepatosplenomegaly and proteinuria steadily increased. The patient was readmitted in March, 1954, when persistent effusions were present in the small joints of the hands, and *x*-ray films disclosed periostitis of the fourth metatarsals and erosions of the metacarpal heads. Corticotrophin was substituted for cortisone, and 20 units a day completely relieved the arthritic symptoms. A rising blood pressure to 210/120 mm. Hg necessi-

tated discontinuation of corticotrophin, but a maintenance dose of cortisone relieved his symptoms and his protein pattern returned to normality.

This remission continued until 1956, when a relapse of the arthritis occurred, involving the wrists, knees, and ankles, despite maintenance cortisone of 50 mg. a day. Hepatomegaly and proteinuria rapidly returned (Fig. 2). The cortisone dose was increased by increments to 150 mg. a day, but knee effusions persisted despite the addition of intra-articular hydrocortisone. Serum electrophoresis again showed the changes seen in amyloid nephrosis (Fig. 3). While on this dose of cortisone a course of triiodothyronine was given for eight weeks in increasing doses up to a total of 480 μg. a day, with little detectable effect on the symptoms or signs of the disease (Table I). The thyroid hormone was therefore withdrawn, and under cover of antituberculous drugs the cortisone dosage was raised to 200 mg. daily. The knee effusion slowly subsided and the E.S.R. fell. By May, 1957, the arthritis was less active, the liver smaller, and the proteinuria dropped to 0.9 g. daily. The blood urea was 30 mg./100 ml., and the serum electrophoretic pattern was again normal (Fig. 3). Maintenance cortisone dosage of 125 mg. daily has enabled the patient to return to full-time work, but the right knee has continued to show mild rheumatoid activity and slight proteinuria has persisted. The liver enlargement is unchanged.

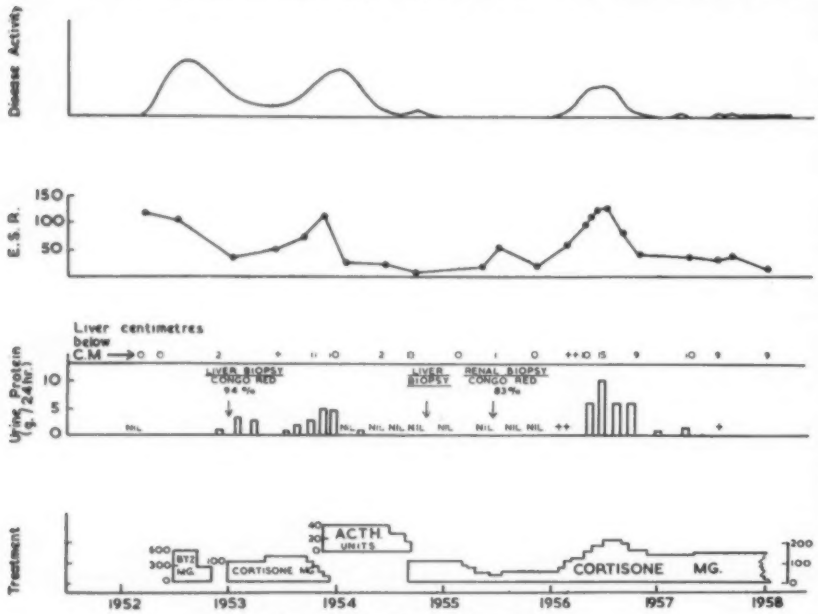
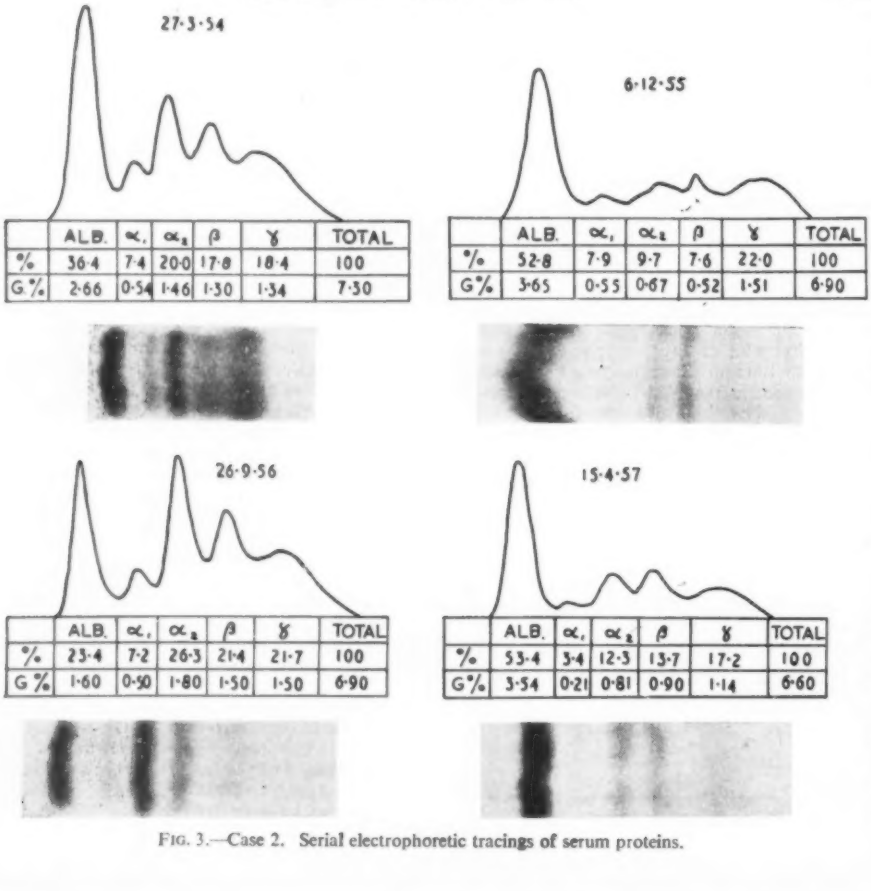


FIG. 2.—Case 2. Course and treatment.



	ALB.	α_1	α_2	β	γ	TOTAL
%	36·4	7·4	20·0	17·8	18·4	100
G%	2·66	0·54	1·46	1·30	1·34	7·30

	ALB.	α_1	α_2	β	γ	TOTAL
%	52·8	7·9	9·7	7·6	22·0	100
G%	3·65	0·55	0·67	0·52	1·51	6·90

	ALB.	α_1	α_2	β	γ	TOTAL
%	23·4	7·2	26·3	21·4	21·7	100
G%	1·60	0·50	1·80	1·50	1·50	6·90

	ALB.	α_1	α_2	β	γ	TOTAL
%	53·4	3·4	12·3	13·7	17·2	100
G%	3·54	0·21	0·81	0·90	1·14	6·60

FIG. 3.—Case 2. Serial electrophoretic tracings of serum proteins.

Comment.—This patient showed regression of the clinical signs of amyloidosis during a remission of rheumatoid disease, coincident with hormone therapy. Proteinuria disappeared and the liver edge regressed 11 cm. during 12 months. Biopsy of the liver and kidney, however, showed that reabsorption of the amyloidosis had not occurred, and relapse of the rheumatoid disease was closely followed by recurrence of massive hepatomegaly and proteinuria. Despite evidence of continued amyloidosis the patient remains in good health *while taking* a maintenance dose of cortisone.

Cases 3 and 4

Two further patients, both females, with amyloidosis secondary to rheumatoid arthritis were treated with steroid hormone in an attempt to reproduce the improvement noted in Cases 1 and 2, but in both of them the dose of prednisolone required to suppress the active joint symptoms gave rise to peptic ulceration and necessitated withdrawal of the hormone. The changes in their clinical and biochemical state during the hormone treatment were minimal (see Table II).

TABLE II.—*Treatment with Prednisolone*

Case No.		Liver (cm.)	Spleen (cm.)	E.S.R. (mm./hr.)	Urea (mg.)	Urine Protein (g./24 hr.)	Alb α_2 Ratio
3	Before treatment	0	0	55	41	4·5	4·0
	After 15 mg./d. for 6 months	0	0	32	46	5·5	4·6
4	Before treatment	1	0	120	25	3·0	1·5
	After 25–30 mg./d. for 3 months	0	0	42	22	4·0	1·45

We have observed the development of amyloidosis in four rheumatoid arthritic patients who had at some stage received treatment with corticotrophin or steroid hormone. In each case, however, the arthritis was of a severe generalized unremitting type, in which amyloidosis is most commonly seen, and at no time had the disease activity come under control with steroid hormone. It was not thought that the hormone had precipitated the development of the amyloidosis. The two patients died in renal failure. In one the cortisone was given only in the five weeks preceding death, when the patient was already in uraemia. In the second, cortisone was administered after the discovery of proteinuria, indicating that amyloidosis was probably already present. Post-mortem examination of both patients showed widespread amyloidosis, which did not differ in any way from that seen in patients not treated with steroid hormone.

In Cases 2 and 3 treatment with triiodothyronine failed to show clinical or biochemical changes suggesting any improvement of the amyloidosis (Table I) during this time.

Discussion

Regression of the clinical signs of amyloidosis during the prolonged remissions described in the above cases suggested that the amyloid deposits in the liver, spleen, and kidneys were undergoing resorption as described by Waldenström (1928). The biopsy from our patients failed to show this. It is known that amyloid is a somewhat inert substance, and both deposition and absorption of the material occur slowly. The rapid decrease in liver size in Case 2 during 1955 was not associated with histological evidence of resorption. Although liver biopsies are not necessarily representative, the apparent increase in amyloid in the second biopsy makes it unlikely that significant resorption had occurred. Perälsalo's (1948) experience is of interest in relation to this point. He reported a case of pulmonary tuberculosis complicated by amyloidosis proved by liver biopsy. Temporary improvement with regression of the signs of amyloidosis occurred and a further liver biopsy failed to show amyloid disease, but deterioration and death soon followed, and necropsy examination revealed extensive hepatic amyloidosis.

In both of our patients there is strong evidence that extensive renal damage has resulted from amyloidosis. Case 1 later developed a typical nephrotic syndrome after two remissions of three years and one year respectively, during which she was free from proteinuria, while in Case 2 the renal biopsy showed amyloid deposits at a stage when the clinical signs of amyloidosis had been absent for one year. During these remissions the Congo-red test remained abnormal in each patient. The exacerbations of the rheumatoid arthritis were in each case accompanied by the rapid reappearance of proteinuria. This is not unexpected in view of the irreversible ischaemic renal scarring seen in the later stages of amyloidosis. Richter (1954) has shown in rabbits that experimental splenic amyloid may be completely reabsorbed, with return to normal histological appearance, when the stimulus to amyloid deposition is withdrawn; however, the renal amyloid lesions remain unchanged.

Proteinuria is an extremely variable manifestation of renal disease and may fluctuate considerably from day to day in the absence of change in the underlying renal lesions. Corticotrophin and the steroid hormones may abolish or greatly reduce urinary protein loss in 60% or more of nephrotic patients (Lange *et al.*, 1957). Lauson *et al.* (1954) have produced evidence that corticotrophin decreases glomerular permeability to albumin in patients with the nephrotic syndrome. Steroid treatment of these patients may result in the disappearance of proteinuria, but, although there may be some improvement in the renal histological picture at biopsy (Galán and Masó, 1957), a considerable number of patients relapse, with reappearance of proteinuria, despite maintenance steroid treatment. It seems likely that the disappearance of proteinuria in our cases may have resulted from this non-specific effect of corticotrophic and steroid hormone on the renal clearance of protein.

The findings in these patients indicate that little reliance can be placed in changes in the clinical signs of amyloidosis. Disappearance of hepatosplenomegaly and proteinuria, with return to normal of electrophoretic patterns and sedimentation rate, may occur despite persistence of amyloidosis. All these signs may rapidly recur with exacerbation of the precipitating rheumatoid arthritis. Despite the failure to demonstrate the resorption of amyloid deposits in our patients there is no evidence that treatment with steroid hormone had a deleterious effect on the amyloid process. The development of this nephrotic state in a rheumatoid arthritic patient with active joint disease would fully justify a trial of these substances.

Summary

Despite experience in amyloidosis secondary to tuberculosis and sepsis, there does not seem to be any histologically proved case of recovery from amyloidosis secondary to rheumatoid arthritis. In two cases the disappearance of clinical signs of amyloidosis was unaccompanied by other evidence of amyloid resorption. Relapse of the rheumatoid disease was accompanied by return of splenomegaly and proteinuria, and biopsy confirmed the continued presence of amyloid in the liver and kidneys. Steroid hormones did not appear to influence the disease unfavourably, and may have induced remissions in the two patients reported.

Triiodothyronine did not influence the clinical or biochemical findings in two patients treated.

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INTESTINAL PERFORATION AND WIDESPREAD ARTERITIS IN RHEUMATOID ARTHRITIS DURING TREATMENT WITH CORTISONE

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Perforations of the small and large intestines in patients under treatment with cortisone have not often been reported, and the few cases recorded usually have had coexisting intestinal disease. Sloan, Briggs, and Halsted (1951) report one case of intestinal perforation, Tulin, Kern, and Almy (1952) three cases, Pessel, Beairsto, Edwards, Rathmell, and Wise (1953) one case, all in ulcerative colitis. Levin, Rivo, Scott, Figueroa, Fred, and Barrett (1953) describe a case of perforation in rheumatoid arthritis with widespread arteritis; Sauer, Dearing, and Wollaeger (1953) one case in ulcerative colitis and two in regional enteritis; Bradley (1954) one case of rheumatoid arthritis without arteritis; Palmer, Mason, and Adams (1955) two cases of diverticulitis; and Gumpel, Lewis, and Thomson (1957) one case of ulcerative colitis.

In the present paper three cases of intestinal perforation are described—one case with perforations in the jejunum and duodenum, one case in the caecum, and another in the sigmoid colon. All three were cases of rheumatoid arthritis under treatment with cortisone, and at necropsy each showed a widespread arteritis.

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Case 1

A 54-year-old man was admitted to hospital in May, 1956, for seven weeks for progressive stiffening of joints. In 1948 he developed pulmonary tuberculosis and was treated in a sanatorium until 1952 with resulting arrest of the disease. In January, 1956, he developed pain in the fingers and rheumatoid arthritis was diagnosed. In May, 1956, he was treated with prednisolone, 30 mg. a day. He was readmitted in December, 1956, and on an attempt to reduce the drug the arthritis became worse, so the prednisolone was discontinued. No lupus erythematosus cells were found. He was readmitted in August, 1957, because he had become bedridden, and was found to have the typical deformities of rheumatoid arthritis, with contraction of the hands, elbows, and knees, and many subcutaneous nodules. He was started on cortisone, 150 mg. a day, which was decreased to 70 mg. a day on September 1. On September 7 his third left finger became gangrenous. The cortisone was decreased to 60 mg. a day on September 10. On September 23 he developed severe abdominal pain, and on laparotomy was found to have a recent perforation 4 cm. in diameter of the sigmoid colon. His course was downhill, and after repair of the perforation he died on October 2.

At necropsy generalized peritonitis was found, with 150 ml. of thick yellow fluid in the abdominal cavity. The lungs contained numerous areas of fibrosis. The heart weighed 310 g., no pericarditis being present. The liver was pale and the kidneys appeared normal. The other organs showed no relevant changes. Microscopy revealed an acute arteritis in about half the small arteries in the heart, pancreas, small and large intestines, adrenals, and psoas muscle. The arteritis consisted (Fig. 1) of a deeply staining eosinophilic material (fibrinoid necrosis) extending through part or all of the artery wall and infiltration of its wall with inflammatory cells, mostly polymorphonuclear leucocytes. The heart, pancreas, small and large intestines, adrenals, psoas muscle, kidneys, liver, testes, and oesophagus showed a few small arteries (Fig. 2) with a grossly thickened fibrous intima and partial disruption of the internal elastic lamina; these vessels were thought to be a healed stage of the arteritis. The adrenals were depleted of fat.

Case 2

A 39-year-old man was admitted to hospital with perforation of the caecum in August, 1957. In 1942 he developed pain and stiffness in the joints of his hands and feet. A diagnosis of rheumatoid arthritis was made, and this pursued a chronic course. He was treated with cortisone in 1949 and was given several courses over the next few years, but details and dosage are not known. In 1955 he became short of breath, and was found to be anaemic, with an enlarged spleen. The spleen was removed and a diagnosis of Felty's syndrome was made. Cortisone was again given, and in August, 1957, he developed severe abdominal pain. Laparotomy was performed and a perforation of the caecum with surrounding abscess formation was found. He developed generalized peritonitis, and four days later a resection of part of his small intestine and caecum was performed. After this he was given cortisone, 50 mg. daily. A faecal fistula and subphrenic abscess supervened and he died one month later.

At necropsy there was generalized chronic peritonitis with an abscess measuring 10 cm. in diameter on the posterior aspect of the liver. The heart weighed 340 g. and there was a moderately acute pericarditis. The adrenals were atrophic. The other organs showed no relevant changes. Microscopy revealed an acute arteritis in the small and large intestines, testes, pancreas, kidneys, liver, and adrenals. A healed arteritis was seen in the heart, small and large intestines, pancreas, and kidneys. The adrenals were depleted of fat and atrophic, and about one-quarter of each was necrotic.

Case 3

A 45-year-old man was admitted to hospital on January 21, 1953, for stiffness of finger-joints and redness of knee-joints. In 1936 he developed stiffness of his finger-joints, which was diagnosed as rheumatoid arthritis, and in 1946 he had a duodenal ulcer, both continuing with remissions. On January 12, 1953, he had a haemorrhoidectomy, and on the 17th his joints became stiffer and red. On admission he was found to have redness of both knee-joints, elbows, and second and third finger-joints, and he was placed on cortisone 150 mg. a day. His joints improved and the cortisone was stopped on January 28; however, moderate albuminuria was detected at this time. On February 3 he was put on corticotrophin 20 mg. a day, which was raised to 40 mg. on the 5th. He became unconscious for 12 hours on February 10. On February 15 he developed abdominal pain. Laparotomy revealed a duodenal perforation, which was repaired. He died the next day. At necropsy generalized peritonitis was found with 3,000 ml. of dark brown fluid in the abdominal cavity. A sutured chronic duodenal ulcer and a recent perforation 0.5 cm. across, 60 cm. from the start of the jejunum, was found. The heart weighed 500 g., with left ventricular hypertrophy and pericarditis. The kidneys were deep red in colour, weighed 300 g. each, and were otherwise normal. The other organs showed no relevant changes. Microscopy revealed an acute arteritis in the large and small intestines, testes, adrenals, and kidneys. An area of recent necrosis 2 mm. across, extending throughout the cortex, was found in the right adrenal. Fat was depleted in the adrenals.

Discussion

Three cases of rheumatoid arthritis have been described, each ending fatally with intestinal perforation and a widespread acute arteritis with fibrinoid necrosis. Many arteries also showed marked intimal thickening, which was thought to be a healed stage of the acute arteritis. The intestinal perforation is not thought to be caused by the arteritis, as gastric and duodenal perforations seen during cortisone therapy are usually without an arteritis, and Bradley's (1954) case of perforation of the large intestine occurred without an arteritis in a patient with rheumatoid arthritis on cortisone. However, it is impossible to exclude entirely the arteritis as a cause, because it was found in the intestine in every one of the three present cases.

The causation of the arteritis is also controversial, as arterial lesions have been described as occurring in rheumatoid arthritis for many years. Kemper, Baggenstoss, and Slocumb (1957), reviewing the arterial lesions in rheumatoid arthritis, state that the following types have been described; perivascular accumulation of cells, vascular infiltration without severe necrosis, and acute arteritis with necrosis of the vessel wall limited to one or two organs—namely, the joints, heart, or subcutaneous tissue. Cruickshank (1954), in a study of 72 necropsy cases, found 11 with a subacute arteritis, sometimes with necrosis; the heart was affected in nine, muscle in three, nerve in five, and trachea, oesophagus, and pancreas in one. A few cases of generalized acute arteritis have been described in which cortisone was not given. Nyström (1953) records one case and Ball (1954) three cases. Therefore it appears that acute arteritis occurs infrequently in rheumatoid arthritis, most often being localized but very occasionally generalized.

However, since the advent of cortisone treatment of rheumatoid arthritis many more cases of generalized acute arteritis have been described; West and Newns (1953) record one case, Levin *et al.* (1953) two cases, Ball (1954) one case, Ogryzlo (1953) an unspecified number, Weinberger (1953) an unspecified number, Slocumb (1953) one case, Finck (1955) one case, and Kemper *et al.* (1957) four cases. Therefore it would seem that widespread acute arteritis can occur in rheumatoid arthritis, but it occurs more often in patients on cortisone. As widespread acute arteritis is uncommon in other diseases treated with cortisone, it appears that patients with rheumatoid arthritis are unduly sensitive to the administration of cortisone. It seems that patients with rheumatoid arthritis have a very slight tendency to develop widespread acute arterial lesions, a tendency which is accentuated by treatment with cortisone.

A possibility to be considered is that the present cases are not of rheumatoid arthritis, but are instances of a disease in which arterial lesions are well recognized and with which arthritis sometimes occurs. The two main possibilities are polyarteritis nodosa and systemic lupus erythematosus; for Friedman, Schwartz, Trubek, and Steinbrocker (1953) have described the occurrence of arthritis in these diseases. However, in the present cases, on careful consideration of their histories and findings, no other diagnosis than rheumatoid arthritis can be made, and the diagnosis of polyarteritis nodosa and disseminated lupus erythematosus is not tenable.

We conclude that the intestinal perforation and arteritis in the present cases are probably separate abnormal reactions to cortisone treatment, and that cases of rheumatoid arthritis are more likely to react abnormally to cortisone therapy than many other diseases.

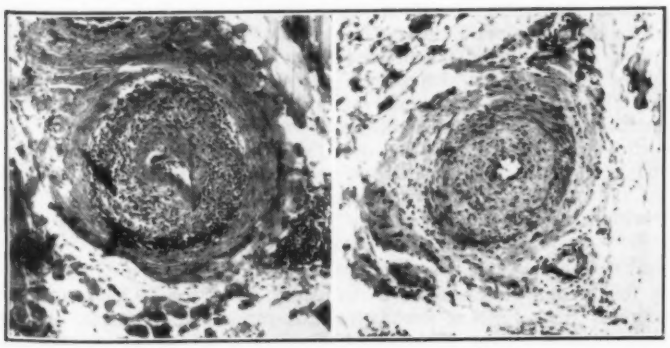

FIG. 1 FIG. 2

FIG. 1.—Case 1. Small artery showing acute arteritis with cellular infiltration in its wall. (H. and E. ×75.) FIG. 2.—Case 1. Small artery with marked intimal thickening. (H. and E. ×75.)

Summary

Three cases of intestinal perforation and widespread arteritis in rheumatoid arthritis during treatment with cortisone are described. Most of the few cases of intestinal perforation previously described in patients under treatment with cortisone have had intestinal disease.

Widespread acute arteritis is rarely found in rheumatoid arthritis, but since the advent of cortisone therapy such cases appear to have increased. It is suggested that cases of rheumatoid arthritis on cortisone have a greater liability than other diseases to develop an acute arteritis.

We consider that the intestinal perforation and arteritis in the present

cases are probably separate abnormal reactions to cortisone which are more likely to occur in cases of rheumatoid arthritis than in other diseases.

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A CONTROLLED TRIAL OF VARIOUS FORMS OF PHYSIOTHERAPY IN ARTHRITIS

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In the field of physical medicine, therapeutic measures are critically assessed in comparatively few centres in this country or elsewhere. Much physiotherapy seems to be determined by an authoritarian approach or by superficial observation based on general impressions—for example, that if the patient does well the treatment must therefore be effective. The methods of quantitative assessment seem to be unknown in many non-teaching hospital departments. In so far as a physiotherapeutic department often contains and demands a great deal of expensive equipment, takes up considerable space, and personnel and patient's time, particularly in the fields of orthopaedics and rheumatism, we have felt that a controlled trial of various forms of physiotherapy would not only be useful in itself but be of educational value within the department.

A number of studies have compared the short-term or immediate physiological effects of various forms of physical treatment, but we wished to ascertain the relative value of various forms of physiotherapy as used in the ordinary way in the department over periods of several weeks in the care of patients with chronic arthritis. We were aware of the difficulties in running a long-term trial, but we did not then realize how formidable they were. It still seems to us, however, that a trial of a realistic nature such as this, conforming to the conditions under which such patients are normally treated, gives information which is of much greater value to the clinician, to the patient, and to the public, than data, more easily arrived at, relating to the immediate physiological effects such as have been published not infrequently in the past.

The questions which the trial was designed to answer were: (1) Which of four forms of physiotherapy (short-wave diathermy, infra-red radiation, faradic stimulation, or paraffin-wax baths) produces the greatest functional improvement during one month's treatment? (2) Is there any significant difference between these treatments and the treatment given to patients on the same basic regime without the additional form of physiotherapy?

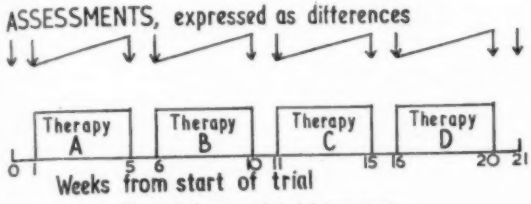
Plan of Trial

The trial was set up to study out-patient treatment of individuals with either rheumatoid arthritis involving the hands or knees, or with degenerative joint disease involving the knees. These joints were chosen because they are the easiest on which to assess function accurately. If other joints of these patients were also affected, they were to be treated but not assessed. The criteria for diagnosis were those operative in the rheumatism unit—that is, for rheumatoid arthritis a polyarthritis of unknown aetiology with pain, swelling, and limitation of joints and a raised sedimentation rate; for degenerative joint disease we accepted clinical and radiological evidence with a normal sedimentation rate. It was planned to select 100 patients consecutively referred to the physiotherapy department for treatment and meeting these criteria.

Instead of comparing four separate groups of patients treated in different ways, we treated each patient with each of the four treatments, so that each patient served to some extent as a control on himself. Because, however, it is known that the order of treatments is important and that in general the first treatment of whatever character given to any patient is usually more effective than the second, the order of treatment was allocated at random to each patient. Each patient therefore received one month of treatment A, one month of treatment B, one of C, and one of D, separated each from the other by one week's rest, but randomized in regard to sequence. For each of the three diagnostic categories (rheumatoid arthritis, hands; rheumatoid arthritis, knees; or degenerative joint disease, knees), a series of envelopes were prepared listing the order of these four treatments and sealed. When, therefore, a patient was selected for the trial and met the criteria, the next envelope in the appropriate one of the three categories was opened; this was intended to make sure that over the group as a whole no particular treatment had a greater chance of being first or last than the other treatments. Thus the patients were selected at random to a particular treatment order, but each patient received all four treatments.

The treatments selected for comparison consisted of: (1) Short-wave diathermy given for 20 minutes three times a week. (2) Infra-red radiation for 20 minutes three times a week. (3) In patients with knee involvement, faradism to the quadriceps 20 minutes three times a week, or, for patients with hand involvement, wax treatment 20 minutes three times a

week. (4) In addition, a fourth group was selected in which the patients were given what we called "cold short-wave diathermy," administered in the same way as ordinary short-wave diathermy but without turning on the current. A warning was given that they would probably not feel any heat. This served as a control group.



Plan of therapeutic trial (see text).

Every patient in each of these four groups was also put on a basic regime of active exercises, assisted or resisted, with calcium aspirin or tab. codeine. co. as required, and splintage as necessary. The active exercises were all given after the treatment on trial. The diagram shows the plan of this trial for a patient whose envelope indicated that he was to start on treatment A, to be followed by B, C, and D in that order. Assessments were made by one of us (D. E. H.) at the points indicated by arrows, before and after each month of treatment. In patients with knee involvement the thigh circumference was measured at a point 3 in. (7.5 cm.) above the superior border of the patella on a line marked by the injection of indian ink. This will not be further discussed, because it was found on assessment that the circumference reflected weight change rather than muscular strength in a ratio of approximately 1 in. (2.5 cm.) increase in circumference to every 14 lb. (6.4 kg.) gained in weight.

The range of movement was measured with a jointed "perspex" angle measure, from bony points marked with indian-ink injection. It is important to note that the angle measure was unmarked. The angle was fixed by a screw, the resulting angle being drawn on paper and then measured with a protractor. This ensured that the actual measurement on the patient was performed without reference to the preceding measurement. Power of extension of the knee from 90 degrees flexion was measured by a weighted boot of the Delorme type in pounds, always starting each session by extending against gravity only and adding by 2-lb. (0.9-kg.) increments. Care was taken that the thighs were parallel to the floor. The time to walk up four standard steps and down again was taken as the mean of two performances. In the same way, the time to walk 20 yards as the mean of two performances was noted with a stop-watch in seconds. For assessment of power in the hands, a mercury manometer attached to a sphygmomanometer cuff was used with the arm in supination and at 90 degrees elbow flexion. The range of wrist movement was measured as before and the time to tie three knots was also measured. This had to be taught and was practised before each reassessment. These assessments were entered on a standardized form.

We planned originally to select 100 patients for this purpose, but owing to various causes a number of these patients did not attend as they should have done over the whole five-months period. We had therefore to continue selection, so that a total of 131 were entered into the trial. Those patients who were unable to attend for the full five-months course were not included in the results. A total of 64 patients were thus excluded. It did not seem that any particular bias was introduced by this exclusion. The reasons for non-attendance are shown in Table I; it will be seen that

TABLE I.—*Reasons for Non-completion of Course*

	Sensitivity to Wax	Intercurrent Disease	Holidays or Moving House	Recovery	Treatment Changed by Doctor	Family Difficulties	No Reason Known	Total
D.J.D.	—	6	3	12	2	4	1	28
Rh. arth.	2	8	4	10	5	3	4	36
Total	2	14	7	22	7	7	5	64

they are very varied. The only troubles caused by this failure to attend were, firstly, the trial was prolonged and further patients had to be taken into it; secondly, it upset the prearranged distribution of treatment orders, so that the initial treatment with one particular measure occurred slightly more often than with others. Sixty-seven completed the scheme and 64 failed to do so. Five of the 67 patients who completed the scheme have also been excluded from the analysis—four because only one knee was affected and this might have affected walking-time and stair time, and one because cerebral arteriosclerosis slowed his reaction to such an extent that it masked the trial assessment.

Analysis of Results

We have taken for analysis of each assessment the quantitative difference between the beginning and the end of each month's treatment, a positive measure thus showing an apparent improvement and a negative one an apparent deterioration. It may be seen from Table II that, in each type of assessment averaged over all four

TABLE II

Group	Assessment	No. of Patients	Stand. Deviation	Mean	Mean/S.E.M.
R.A. knees (18 patients)	Range ..	18	11·30	1·32	0·99
	Power ..	18	6·12	1·93	2·67*
	Stair time	18	14·17	1·31	0·78
	Walk ,,	18	25·65	2·07	0·69
D.J.D. knees (26 patients)	Range ..	26	10·89	1·81	1·74
	Power ..	26	5·57	2·05	3·85*
	Stair time	26	8·79	2·36	2·82*
	Walk ,,	26	8·82	1·30	1·54
R.A. hands (33 patients)	Range ..	33	20·55	0·19	0·11
	Power ..	33	36 00	1·31	0·42
	Knot time	33	26 69	7·81	3·36*

* Significant (t test). Note—all positive. S.E.M. denotes standard error of the mean.

treatments, the mean differences are positive for all groups of patients. These means are also shown as ratios of the "standard error of the means" to examine their magnitude in relation to the inherent variability of the particular measurements. In four instances (starred in the table) the ratio mean S.E.M. is greater than 2, indicating that in these cases the apparent improvement is statistically significant at the 5% level.

It appears, therefore, that there is a demonstrable improvement in some of the tests and that the others, while not statistically significant individually, all have the same sign, suggesting that there is, in general, an overall improvement from the beginning to the end of the month. It is necessary now to examine whether the improvement is related to the particular treatment.

Table III details the results of the individual treatments. Treatment A was the dummy or "cold"

TABLE III

Group	Assessment	A "Cold" S.W.D.	B S.W.D.	C Infra-red	D Wax or Faradism
R.A. knees (18 patients)	Range ..	−0·62	0·46	−0·40	0·56
	Power ..	−1·37	0·32	0·32	0·72
	Stair time	0·09	0·76	−0·20	−0·64
	Walk ,,	0·49	0·69	1·17	−2·34*
D.J.D. knees (26 patients)	Range ..	−0·24	−0·49	−0·09	0·81
	Power ..	0·91	−0·30	−0·80	0·20
	Stair time	−0·65	−0·09	1·49	−0·75
	Walk ,,	−1·07	0·66	1·43	−1·02
R.A. hands (33 patients)	Range ..	−1·35	0·57	−0·35	1·13
	Power ..	−0·01	0·54	−0·35	−0·18
	Knot time	−0·90	0·78	−0·41	0·54

* Significant (t test).

short-wave diathermy plus the basic regime alone, whereas B, C, and D had a special treatment in addition to the basic regime. These figures have been analysed by approximate analysis of variance and no evidence could be found of any significant difference between these four treatments. To illustrate the results most clearly, the values given in Table III are "scores" instead of actual measurements. The scores may be looked upon as deviations from the average improvement shown in Table II. "Scores" are the "standardized" differences of each treatment mean from the overall mean of all treatments for the particular assessment and are obtained by expressing the difference of the treatment mean from the overall mean as a ratio of the standard error. Thus for the rheumatoid arthritis knee group of patients the range assessment showed that treatments A and C were below the average while B and D were above the average. The advantage of presenting them in this way is that statistically significant values (scores greater than 2) can be seen at a glance. In fact, only one value was significant, and this may well be a chance effect among so many comparisons. In general, over the three diagnostic categories, treatments A and C are not quite as good as B or D, since there are eight and seven minus signs as against three and five minus signs respectively, but none of these differences between treatments reaches positive significance levels.

When we come to examine the results of order of treatment in the same way (Table IV) it will be seen

TABLE IV

Group	Assessment	Order of Treatment			
		First	Second	Third	Fourth
R.A. knees (18 patients)	Range ..	1·45	−1·08	−0·67	0·29
	Power ..	−0·21	−0·57	−0·08	1·66
	Stair time	−0·43	1·18	−1·39	0·64
	Walk ,,	0·12	1·58	−0·43	−1·28
D.J.D. knees (26 patients)	Range ..	−0·43	−1·07	0·68	0·81
	Power ..	0·20	0·45	−0·76	0·11
	Stair time	2·00*	−1·73	0·04	−0·30
	Walk ,,	1·59	−0·62	0·09	−1·05
R.A. hands (33 patients)	Range ..	−1·29	−0·28	−0·21	1·78
	Power ..	2·02*	−1·98	−1·34	1·30
	Knot time	3·00*	−0·77	−1·40	−0·83

* Significant (t test).

that the first treatment scores three positive significant standardized differences, and in fact analysis of variance also shows that this is significant for the patients with rheumatoid arthritis affecting the hands. The second and third treatments, whatsoever they consist of, do not produce as much improvement, since the number of minuses in the second and third is higher than in the first and fourth treatments.

Summary

We may conclude that, although in each of the diagnostic categories there was some improvement after treatment compared with the state before treatment, this occurred more commonly in the first treatment, whatever that consisted of, and that when short-wave diathermy, infra-red, and Faradism or wax treatment are compared with a dummy exposure to short-wave diathermy, no significant difference is seen. This means that if there is a difference between treatments it is too small in relation to the variability of the group, and of the measurements, to be distinguishable in this number of patients from that due to chance variability. It must be remembered that all patients were on a good basic regime of exercises, analgesics, splintage, and encouragement, and it seems possible that the general improvement noted could in fact be due to this basic regime.

It should be realized that controlled trials like this do not prove that such and such a treatment is no good. Results merely indicate that, although improvement has occurred in certain measurements and in certain groups of patients, the variability due to measurements, due to patients, and due to chance is too large for effects due to differing treatment to show in the series under consideration. We have not felt that it was ethical to carry a group of patients who were not on a basic regime of analgesics, exercises, and splintage, and indeed it would not only be wrong but impossible to persuade people to attend for five months on such a basis. We have felt, on a basis of general impressions only, for a number of years, however, that the most useful measures in the field of physiotherapy were those which maintained muscle power by active exercise, and those which maintained joint movement, good posture, and the co-ordination of movement. These ends can be achieved by assisted and resisted exercises, encouragement, splintage, the use of analgesics, weight reduction when necessary, and postural re-education. And, while these other measures which we have discussed may be useful adjuncts, this present control trial has not indicated that they are significantly better than dummy treatment.

We are grateful to Miss Morris, superintendent physiotherapist, and to Dr. George Fearnley, for help both at the planning stage and later, and to the Board of Governors of Hammersmith Hospital for a grant to one of us (D. E. H.) specifically for this study.

Home accidents cause more deaths than road accidents. In recent years there have been over 1,000 home accident deaths annually in Scotland. It is clear that accidents in the home form one of the major hazards of present-day living, and an analysis of such accidents suggests that a good many are due to faulty design of certain features in the home. A booklet published by the Department of Health for Scotland has been issued to help pinpoint the various risks which arise in the home and suggest how they can be minimized. It has been prepared for architects and other technical officers as well as for members of housing committees and others interested in home safety. They will all wish to satisfy themselves on how far the safety provisions mentioned apply to the houses for which they are responsible. Safety is an essential factor to be kept in mind in the design and construction of new houses, and it is with this aspect that this booklet is primarily concerned. Some of the recommendations, however, could be applied with advantage to existing houses—in particular, the provision of fireguard fixings ("Designing for Safety in the Home," H.M.S.O. Price 1s. 3d.).

PERIODIC PSYCHOSES*

BY

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The word " period " is most commonly used in medicine to describe the phenomenon of menstruation. " Periodic disease " is a name given to cases of regularly recurrent and intermittent episodes of fever, or oedema, or arthralgia, or gastric pain and vomiting, in which the attacks continue for many years without further development in otherwise healthy individuals (Reimann, 1951). By periodic psychoses I mean those mental illnesses which, upon study over a period of time, show a similar intermittent regularly recurring course, periods of depression or hypomania alternating with days or weeks of normal mood, attacks of excitement or agitation, episodes of stupor or confusional symptoms striking regularly by the calendar in seemingly mentally healthy or nearly healthy individuals. Such cases may be labelled manic-depressive illness, catatonic schizophrenia or schizo-affective state, sometimes even hysteria or psychopathy. Some occur in every mental hospital, though not always recognized as periodic, particularly when the outbursts or attacks come at longish intervals, perhaps every six weeks. However, they are easily discovered when looked for.

A periodic psychosis may be suspected when a patient is admitted and discharged twice or thrice in a year, since the regular intermittent nature of the illness means that there will be a fairly quick spontaneous recovery in hospital, and a relapse at home as soon as the next attack falls due. A chronic patient who, though usually well behaved, has times when he becomes aggressive or restless, or stays in bed all day, may prove on closer inquiry to be showing such behavioural change quite regularly and even predictably by the calendar. Nurses of experience are often much more aware of such patients, particularly in the back wards, than are the medical staff. In women, so-called menstrual psychoses must be suspect. Of course not all who suffer from periodic mood swings or other regularly intermittent psychiatric disability are in hospital, but exact information about these people is difficult to come by.

Establishing the Periodicity

The first step in any suspected case of periodic psychosis is to establish the period, the length of time between the onset of one attack, and the onset of the next. Where the medical notes give no guidance to the precise dates of past attacks the daily and nightly hospital ward reports, which are usually stored for a number of years, may be searched with profit, particularly if some sedative such as chloral or paraldehyde had to be given as an extra during the attack, since the use of a drug is fairly certain to be recorded. Or the report may indicate the patients kept in bed each day. If the illness is periodic, the dates of onset will fall approximately the same number of days apart, with occasional irregularities, rather like the menstrual cycle. Sometimes there is a gap twice or thrice the fundamental interval, or some other simple multiple, because one or more attacks have been missed without upsetting the fundamental rhythm of the disease.

Fig. 1 illustrates these points: the episodes, described as schizophrenic, are marked as black rectangles. During these episodes the patient stayed in bed, mumbled to himself, appeared to be hallucinated, showed peculiar mannerisms, was unable to reply intelligibly in speech or in writing to questions, and was restless and noisy at night. Between them he was up and about helping the nurses, in a competent and reliable manner, to run the ward, and was able to converse quite easily. He was in his early thirties when admitted to hospital, and in his old age became deaf and blind and bedridden. Nevertheless his attacks still continued with much the same frequency and duration as before. The earlier ones were charted from the data in the medical notes, the later ones from the ward records of sedation at night. One finds in such cases that restlessness at night and overactivity by day often precede by two or three days the full psychotic attack, and that there may also be a restless night or two when the attack has finished; this explains the slightly longer rectangles in 1956, based on the sedation record. The occasional gaps in the rows of black rectangles are due to the missed attacks.

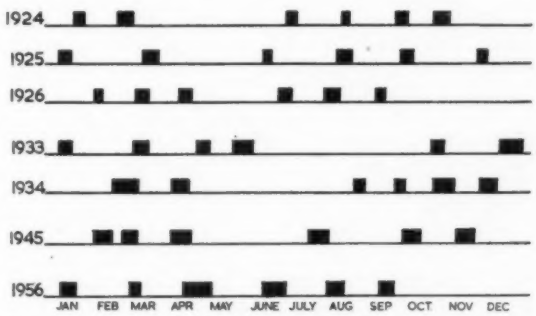

FIG. 1.—Episodes of schizophrenic catatonic disturbance in one patient over a number of years (the years not charted were similar). Some of the apparent gaps are likely to have been brief spontaneous remissions, others may have been a failure to record attacks.

There is a slight tendency for these gaps to be commoner in spring and summer, as Gjessing (1953) notes in his cases of periodic catatonic schizophrenia. I have found them in nearly all the cases I have studied, no matter what the clinical picture of the attack (Crammer, 1957). The most striking fact Fig. 1 shows is the stability of the disease: after 32 years it still ran on in the same old way, neither greatly worse nor greatly better. This is a characteristic of periodic psychoses: once the periodicity is established they do not develop further and produce fresh signs or symptoms. The most that happens is a quantitative change in the severity of some or all of the manifestations whose pattern makes the full attack.

I want to emphasize that such periodic cases occur in both sexes and in every hospital, albeit they are only a small minority of the in-patients. Such cases provide excellent opportunity for therapeutic test. Each patient continually runs through his cycle of behavioural and psychic change, and in any one individual the attacks are all alike, so that he can serve repeatedly as his own

*Read to the Section of Psychiatry at the Annual Meeting of the British Medical Association, Birmingham, 1958.

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control. In studying the effect of a drug, for instance, one can discern which items of the clinical picture are altered and which untouched, and on stopping the drug see the full-blown clinical attack reappear, only to be altered when the drug is given again.

A periodic psychosis also offers the best opportunity in psychiatry for the discovery of a physical basis to mental symptoms and signs, that is to say, for finding some physical sign or pathological test helpful in diagnosis and in predicting the outcome of treatment, or some metabolic abnormality affecting the brain which is directly responsible for some or all of the symptoms.

Physical Pathology

The physical pathology of the periodic psychoses seems their most exciting aspect. The remainder of this paper is a brief view of this subject from general clinical study, from physical examination, and from metabolic experiment.

A survey of many cases gives at once a picture of diversity: diversity in the clinical pattern of the attack in different cases, diversity of rhythms, diversity in age of onset. While a four- or six-weekly rhythm seems not uncommon, shorter cycles are also found. Menninger-Lerchenthal (1950) found 52 cases in the literature with a two-day cycle, alternate days overactive and listless, for instance (see also Richter, 1938), and von Stockert (1957) has added another. These cases were variously diagnosed as schizophrenia or manic-depressive insanity, periodic catatonia, melancholia, and even neurasthenia. The age of the onset was in the twenties, the thirties, the forties, and even in the sixties and seventies. In some the condition was thought to be post-encephalitic, or syphilitic, or arteriosclerotic in origin; in others the result of a fright or a time of great anxiety; in yet others no preceding factor could be discovered.

Often the illness begins as an endogenous depression, or as schizophrenia, and the characteristic periodicity appears only after several months or a year or two. The clinical picture of the single attack in the fully established case is nearly always biphasic and shows first an episode of overactivity and then one of underactivity as its essential feature, whatever the diagnostic label. In the former the patient is restless and talkative and may be euphoric, but may show stereotyped thinking and behaviour. In the latter he is usually quiet or even stuporous, with loss of all feeling, has difficulty in concentrating and in volition, and may have fleeting paranoid ideas.

Different individuals show these various elements in very different proportions, so that one may apparently have recurrent attacks of mania only or of catatonic excitement only, another a series of attacks only of depression or stupor. However, close examination usually shows the other half of the biphasic pattern to be also present in minimal form. For example, in the case of a man of 75 with recurrent stupors (Crammer, 1957, Fig. 1) there was in fact a day or so's extremely mild talkative fidgetiness preceding each stupor by a few days. Fifty years earlier this man had suffered from recurrent excitements. With the passage of years these became less intense, and the brief quiet period after each attack enlarged and deepened, till finally he suffered from full stupor. Barnes (1909) reports the case of a man who took 16 years to accomplish this full changeover, which from published reports apparently occurs only in one direction, towards quieter attacks.

Within the biphasic outline of the acute attack the pattern is sometimes complex, involving shorter episodes of agitated or confusional behaviour for instance, and yet the whole pattern is repeated in sequence each time. Such atypical psychoses (neither truly schizophrenic nor manic-depressive) were separated off by Schröder (1926) as "degeneration psychoses" and by Kleist (1928) as "motility psychoses" and "confusional psychoses." It is important to understand that a periodic psychosis cannot be recognized as such at a single clinical interview, and only with difficulty after an acquaintance of a week or two. The simple and sure method is by the periodicity, which means a good history or at least a few months' recordings.

I have said that each attack is often a complex sequence of events, yet it is one which has an all-or-nothing aspect to it; if it is missed it seems to be missed completely. This sequence is true for the physical phenomena, as well as for the mental. The patient may complain at some time of thirst, or vague abdominal discomfort, may have difficulty in passing urine, may develop a skin rash, and of course may show changes in facial appearance and eyelid motility, in sleep, in appetite, and in bowel habit. But these phenomena, if they occur, may only do so for a certain time within the whole sequence of the attack, and recur every attack only at the same relative time, peculiar to that case. If the attack is not carefully followed day by day to its end, these peculiarities may be missed. The same is true of such physical measures as pulse, blood pressure, temperature, and body weight. The total psychotic attack is elaborately orchestrated. Even where an attack appears clinically uncomplicated—for instance, a stuporous phase—drug experiments suggest cerebral changes while the patient's behaviour remains static and unchanging. It is well known that intravenous amylobarbitone sodium will awaken the stuporous catatonic. In the periodic case different doses are required on different days to produce the same effect. The depth of stupor varies on this measure, when clinically it appears level.

Descriptions of two cases we have been studying in Birmingham will illustrate these general statements.

Case 1

A man aged 49 has been in hospital for 10 years with a six-day cycle predominantly manic-depressive in type. Prior to this he seems to have been well, though probably of low intelligence to judge by his employment record. His illness began at the age of 38 with a manic attack which cleared. He was discharged home but a week later was readmitted again in mania, and has been in hospital since. It is not known exactly when his illness became cyclical, but records for the past five years show that it had not changed in that time, presenting always an uninterrupted succession of cycles each six to seven days long and consisting of about two days of a semi-stuporous state and four days of increasingly cheerful talkative overactivity.

In detail the cycles run like this. During the semi-stupor he sits all day staring into space, with a rather woebegone expression, doing nothing and saying nothing. To all questions he replies "yes," "no," or "dunno" in a low voice. He understands all instructions, but he is slow in all his movements. He eats a normal quantity of food, but very slowly. We have been able to awaken him temporarily from this state by intravenous injection of methyl phenidylate ("ritalin"), and he then passed briefly through a phase in which he expressed the view that his case was hopeless. Over a period of hours the semi-stupor begins

to lighten. His expression becomes more alert, his responses quicker; he may pick up a newspaper and gaze at it; he begins to speak in a normal voice, single words, brief sentences, and, finally, may even venture an occasional spontaneous remark. He begins to smile.

Then there comes the moment when he stretches his arms and stands up, and his overactive phase has begun. For the first day or so he is able to walk a little, to sit down at times, to keep quiet on request, but he is soon walking about endlessly, with a mounting pressure of talk, buttonholing passers-by, laughing and joking. He stays awake all night, talking, singing snatches of songs. His talk becomes progressively loaded with obscenities and more erotic in content; he makes claims to being the greatest violinist in the world and the heir to wealth; but the range of his ideas is very narrow, and they are similarly and repetitively expressed in each cycle. As the hypomania reaches its height, his talk becomes so rapid that the words are slurred, some even omitted altogether. He talks endlessly and no longer requires any sort of audience. His expression ceases to be cheerful and smiling but becomes anxious and haggard. Then his talk changes more and more into mutter, ceases to have any pressure behind it; he walks up and down more slowly, smacking his lips; his attention becomes difficult to attract, and his answers to simple questions are erroneous. Finally he sits down, and the monosyllabic quiet phase has begun again.

Various bodily functions show linked cyclic change. Appetite remains almost constant throughout and fluid intake is steady—he refuses an extra drink even in his lip-smacking phase. But his bowels act only on the first two days of each overactive phase, when he sometimes complains of abdominal discomfort. His urine output shows a polyuria in the overactive phase and an oliguria during semi-stupor. Further, there is a period of difficulty in starting micturition, even with a full bladder, during the day of muttering that precedes the onset of semi-stupor, before the oliguric phase sets in, while one of the first signs that in a few hours he will liven up again is the sudden onset of the polyuria which precedes the overactivity. Two other physical signs are important. His pulse rate, counted resting in bed, shows large swings that bear no relation to his *degree* of overactivity (Fig. 2). His body weight measured daily shows a cyclic variation of about 5 lb. (2 kg.), rising during oliguria, falling during polyuria. By calculation and experiment we have been able to prove that his weight gain represents an increase in body water, and his weight loss is largely accounted for by excessive urine formation (Fig. 3).

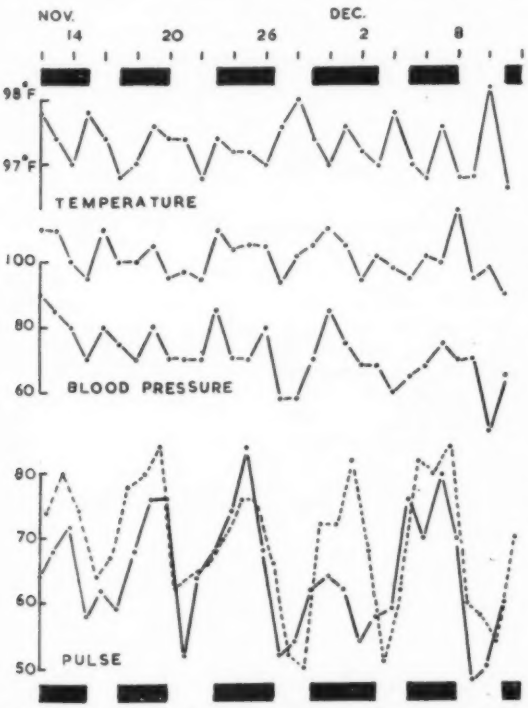

FIG. 2.—Case 1. Change in pulse with mental change: the pulse was taken in bed before rising in the morning (continuous line) and after retiring at night (dotted line). Active mental phases marked as black rectangles, the gaps between represent semi-stupor.

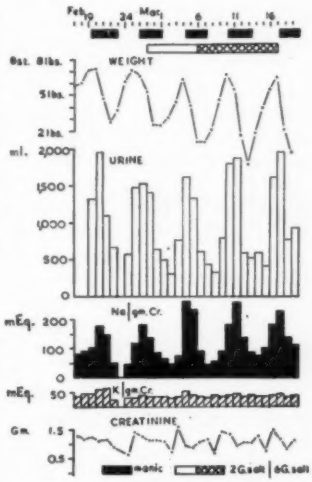

FIG. 3.—Case 1.—Fluctuation in body weight, with associated polyuria and oliguria and variable sodium excretion. Black rectangles represent active phases. Sodium and potassium expressed as per gramme of creatinine present in each urine specimen.

Case 2

A man aged 48 first became ill in 1940 with an attack of depression, from which he recovered. It recurred in 1948 and lasted with variation in depth until in 1952 he had his first manic attack. Since then he has had a cyclic illness, approximately two weeks manic and two weeks depressed, with a brief normal phase between each attack, so that the period from the onset of one manic phase to the onset of the next is about six weeks.

The manic phase begins suddenly. One day he is normal, the next he gets up in cheerful, smiling, talkative mood, which slowly warms up over a number of days with increasing overactivity and pressure of talk, ever-easier joking, laughter, and sociability, and some flight of ideas, and then slowly declines again. There are three or four approximately normal days, and then he becomes gradually but noticeably quieter, speaks only when spoken to, may have difficulty in understanding a question or in finding the answer to it, shows less spontaneous activity, and is inclined just to sit and look gloomy. This goes on for about four days. Then, quite sharply, a new phase is interposed. He stays in bed and refuses to get up, saying he cannot make up his mind about anything. He is restless in bed and picks at the sheets, he talks easily again and replies promptly and correctly; he smiles often, but his spirits are neither up nor down, but blank. After another four days this phase ends, and for about a day he appears suspicious and easily frightened, but denies any delusional ideas. He is quiet again, complains that everything costs him a great effort, and is slow. Gradually he improves, though he complains of difficulty in concentrating for a long time. He has about a week clear, and then the cycle resumes.

Bodily investigation shows no change in appetite, no striking change in bowel rhythm, though at the height of his depressive phase there is constipation. There is possibly a brief complaint of thirst during the body weight minimum in this phase. Pulse rate shows no cyclic change. Body weight remains steady during the overactive phase, and drops suddenly, about 5 lb. (2 kg.) in all, just before the onset of the smiling restless depression, recovering itself in the tail of the depression. These weight changes are accompanied by polyuria and oliguria respectively, and must represent changes in body water content.

Comment

In both cases when there is polyuria there is also a large loss of sodium and chloride in the urine, and in fact the magnitude of the body weight change seems to depend in part on the level of salt in the diet. Fluctuations in body weight have been noted as part of the attack in other periodic psychotics (Rowntree and Kay, 1952; Gjessing, 1953).

Scattered in the literature are reports of cases where mental change and episodic polyuria are associated. Klein and Nunn (1945) reported a case very similar to our six-day cycle man. Broser (1951) observed a man with approximately monthly disturbance of consciousness and brief coma, associated with oliguria, rise in body weight, and then a polyuria and weight fall, which he ascribed to a hypothalamic lesion. Biemond (1949) also described two cases of this sort. It seems not unlikely therefore that these sudden changes of body weight are the result of a hypothalamic disturbance in the course of mental illness, leading to under- or over-secretion of anti-diuretic hormone, and possibly also similar variation of an adrenocortical salt-retaining hormone.

Aldosterone is very difficult to measure at present, but 17-oxosteroids (17-ketosteroids), and the 17-hydroxycorticoids which mostly represent hydrocortisone secretion (Appleby *et al.*, 1955), can be measured fairly satisfactorily. We found the 17-oxosteroids to be a very insensitive indicator of adrenal function; but the second group of steroids fluctuates cyclically in both our patients, being below their normal in the overactive state, and above it during the depressive phase (Fig. 4). This agrees with the finding of Rizzo *et al.* (1954) that adrenal cortical function was low in a manic woman and returned to normal as she recovered, although her glands were normally responsive to injected corticotrophin throughout her illness. The adrenal dances to the tune called by the hypothalamic-pituitary system. During the overactive phase the tune is soft, in the quiet phase it is loud.

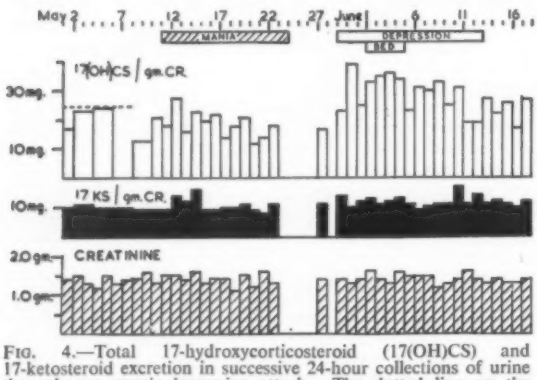

FIG. 4.—Total 17-hydroxycorticosteroid (17(OH)CS) and 17-ketosteroid excretion in successive 24-hour collections of urine through one manic-depressive attack. The dotted line on the left shows the average daily 17(OH)CS output during the previous month, when, exceptionally, the patient remained mentally normal.

Discussion

The painstaking work of Gjessing, in which he improved on the experiments of Pighini (1909) and Pighini and Statuti (1910), demonstrated conclusively that periodic catatonics show a cyclical retention and excretion of nitrogen in the form of urea. Gjessing's work unfortunately requires special facilities; the present paper concentrates on observations which can be made anywhere where there is conscientious nursing, a weighing machine, and a measuring cylinder; or at the most the facilities of an ordinary hospital laboratory. Further it concentrates on biochemical factors which may play a part in producing mental symptoms. It is well known that shifts in sodium and water produce mental symptoms. It is also known that adrenal cortical steroids may have such an effect. Since changes in both these chemical factors occur during the acute psychotic attack it is possible that they are responsible for part of its symptomatic pattern.

One can conceive of the mechanism of a periodic psychosis in three distinct parts: (1) the pacemaker, which sets the rhythm—only at regular intervals is a psychotic attack possible; (2) some factor which is required for the attack to be fired off; and (3) the symptomatic pattern of the psychotic attack, in which there is an ordered sequence of events, one physiological disturbance perhaps provoking the next—for example, a failure of secretion of enough antidiuretic hormone at one stage might result in cerebral dehydration at the next stage, and a fresh set of symptoms while this lasts. On this basis thyroid in a very large dose, known to be an effective treatment in periodic catatonia (Gjessing, 1935; Gornall *et al.*, 1953), might act on the second factor, while chlorpromazine seems to act on the third part of the mechanism. We may hope that by pharmacological and biochemical analysis of this third part—the pattern of repeating psychotic attack—to test the hypotheses that electrolyte, water, and steroid changes are responsible for different parts of the symptom complex, and eventually perhaps to apply the knowledge gained to the study of non-periodic psychoses.

The single greatest need in this field of psychiatric research is that more work should be done, more cases studied by more people. I hope that what I have said may have done something to show that chronic patients, still unfortunately often a neglected group clinically, are worthy of careful study, and that this study can be carried on wherever people are willing to undertake it, without necessarily employing expensive apparatus or technical staff.

Summary

Patients suffering from periodic psychoses occur more commonly than is usually recognized. The illnesses are characterized by brief episodes of mental symptoms recurring regularly, often at monthly or six-weekly intervals, in both sexes. Their special importance is their suitability for research. A brief account is given of some leading clinical features. Some physical and biochemical findings in the two cases reported show how even with simple methods information useful for understanding the physical pathology of psychosis can be obtained.

I am grateful to Dr. J. J. O'Reilly and the medical and nursing staff of All Saints' Hospital, Birmingham, for the whole-hearted way they have aided our investigations.

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TRIFLUOPERAZINE DIHYDROCHLORIDE ("STELAZINE") IN PARANOID SCHIZOPHRENIA

BY

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Experience of phenothiazine derivatives in this hospital had prior to November, 1957, been mainly confined to chlorpromazine, which had been given in doses of up to 850 mg. daily together with electric convulsion therapy (E.C.T.). On the whole it can be said that some relief in symptomatology was obtained in patients with chronic schizophrenia, rather better success in patients suffering from involutional paranoid illness, but the results in cases of acute recent schizophrenia were minimal to moderate and did not obviate the necessity for insulin coma treatment (I.C.T.). It would be fair to criticize our experience with chlorpromazine in that perhaps we were too cautious, as better results have been reported with intensive chlorpromazine plus E.C.T. (Ollendorff, 1958). Nevertheless it appeared that a drug of similar action, more powerful, less toxic, and simpler in its administration, might give better or equally good results without the necessity for E.C.T. or, in acute cases, without the need for I.C.T.

Trifluoperazine dihydrochloride ("stelazine") was reputed to be such a drug. It is derived from prochlorperazine by the substitution of a trifluormethyl group for the chlorine atom in the 2 position of the nucleus. According to the manufacturers it is reputed to be four times as powerful as prochlorperazine and between nine and ten times as powerful as chlorpromazine in blocking conditioned responses in animals.

In November, 1957, a trial of trifluoperazine was begun and its effect tested on a series of patients suffering from acute and chronic paranoid schizophrenia. The patients were treated under the conditions normally applying in this hospital, and no other treatment was given during the experiment except occasional night sedation, and all proceeded with the normal programme of rehabilitation.

The results of treatment in the first 50 patients so treated in the first nine months of the experiment are here recorded. They were divided into two groups.

Methods and Material

Group A.—There were 30 male patients suffering from chronic paranoid schizophrenia who had been in this hospital for a minimum period of two years. All had previously been treated by standard methods, such as I.C.T. and E.C.T., and had been given a prolonged trial with chlorpromazine and, in many cases, other tranquillizers available at the time. None of these treatments had materially altered the clinical picture. The duration of the illness varied from two to fourteen years.

Group B.—There were 20 patients admitted during the first attack of schizophrenia of less than six months' duration who had not had any previous treatment. They were admitted with a recommendation for I.C.T. by other consultants, and when initially examined in this hospital were thought to be cases that would normally have proceeded to I.C.T.

Treatment and Dosage.—Treatment was begun by suspending all other drugs. It was continued by administering 5 mg. of trifluoperazine daily for the first three days, thereafter increasing by 5 mg. daily at three-day intervals until gross side-effects appeared or a satisfactory therapeutic effect had been obtained. When the symptoms had been controlled by trifluoperazine the dosage was reduced to a maintenance level, on which patients were completely free from side-effects and at which the therapeutic effect seemed maximal. The maximum dose used was 45 mg. daily and the average maintenance dose 20–25 mg. daily. Those discharged have been maintained on dosages varying from 5 to 20 mg. daily.

Results

Assessment of the effect of trifluoperazine was made on the patient's capacity towards adjustment to normal social surroundings. These results are shown in the accompanying Table in terms of the degree of deterioration before and after treatment.

Group		(a)	(b)	(c)	(d)
A	Before treatment	26	4	—	—
	After " ..	9	12*	4	5
B	Before " ..	14	6	—	—
	After " ..	—	6†	—	14

* Two of these are fit for discharge but waiting placement.
† Three of these six made good initial improvement with trifluoperazine but proceeded to I.C.T. on the advice of other psychiatrists before trifluoperazine was given a full trial.
(a) Incapable of social living and requiring constant observation. (b) Able to adjust to social living in the hospital community (including parole, short leaves of absence, etc.). (c) Discharged from hospital and able to adjust socially but incapable of earning a living. (d) Discharged from hospital with return to full employment.

Follow-up.—All patients discharged have continued with a maintenance dose. No patients in Group B have reported a relapse. Three in Group A showed a return of symptoms when they had difficulty in obtaining the drug, but they quickly responded when the drug was recommenced. All have been out of hospital for from five to nine months.

Side-effects.—The only side-effects noted were, in order of frequency: drowsiness, Parkinsonism, increased motor restlessness, and increased salivation. No significant alterations were observed in blood pressure, white-cell counts, liver-function tests, or urinary analysis. Drowsiness and salivation occurred on dosages from 10 mg. daily, increased motor restlessness from 15 mg., and Parkinsonism of 20 mg. and above. The most troublesome side-effects, from the patients' point of view, were drowsiness and motor restlessness. The side-effects

were treated symptomatically by such drugs as amphetamine, barbiturates, and antihistamines without benefit. Benzhexol hydrochloride ("artane"), in doses of 6–8 mg. daily, proved effective in eliminating Parkinsonism and in greatly decreasing motor restlessness.

Discussion

Group A

We recognize that improved capacity for social adjustment is dependent on symptomatology, but it was interesting to note the effectiveness of trifluoperazine on specific symptoms. In general we found that the greatest effect was on aggression and general overactivity. Next in response were auditory hallucinations, then delusions; least of all affected were such symptoms as inability to concentrate, incapacity for sustained thinking or effort, abstract thinking, and comprehension in those who did not fully respond. If hallucinations and delusions did not clear up altogether they usually became less intense and the patients less troubled by them. There was often a remarkable degree of return of insight, and we were impressed when those patients who were relieved of their symptoms spontaneously attributed the improvement to the drug. The nursing staff and relatives were unanimous in describing the better rapport they were able to obtain with patients.

In general the improvement was gradual, but once the improved patients were able to graduate to a higher level in the programme of rehabilitation progress was rapid. This was to be expected. We believe that an adequate programme of rehabilitation remains a fundamental approach to the treatment of schizophrenia and that any physical method of treatment that will not only make such a programme more acceptable to a patient but make the patient more acceptable to others has a valuable place in psychiatric treatment.

We were unable to come to any conclusion on why some patients improved and others did not, except in the case of three of the patients who had had prefrontal leucotomy and who failed to show any response—an observation that has been made in the treatment of chronic katatonic schizophrenia in this hospital with prochlorperazine ("stemetil") (Storey, 1959); and Ollendorff (1958) quoted 11 leucotomized cases of chronic schizophrenia that had failed to respond to intensive chlorpromazine and E.C.T.

We cannot understand the findings of Forrester (1958). It is noted that eight of her cases had been leucotomized and two were oligophrenic, and we would not have expected improvement in these. She does not classify the type of schizophrenia in the other 15. The severity of the side-effects she quoted are very different from our experience and the experience of Madgwick *et al.* (1958), Milligan (1958), Rudy *et al.* (1958), and others with whom we have discussed the drug.

In our patients the only side-effect that gave rise to anxiety was motor restlessness. Patients were very aware of it and disturbed by it. Two patients with chronic schizophrenia, both of whom had a compulsive desire to escape from the hospital, became so restless that one jumped from a second-floor window and another jumped down several steps, fortunately without serious injury. Neither had any suicidal intent. This restlessness makes us feel that, certainly in large doses, treatment should only be carried out initially under good day-to-day observation. As we are becoming more familiar with the drug we find that we have been better able to control restlessness, and we are now less worried about it. Parkinsonism is so easily controlled that no anxiety was felt about its occurrence.

Group B

The results of treatment in this group were surprisingly good. A similar pattern of response was found as with chronic patients, except that the response was more of a total one and all groups of symptoms tended to disappear more simultaneously. In those who had lost it, insight returned at a very early stage. All those discharged have maintained their improvement and have continued to take a maintenance dose of the drug. Comments that we have made on side-effects in Group A apply equally to Group B.

Comparison with I.C.T.

A comparison with the results of insulin treatment is desirable. For this purpose we have examined the results of I.C.T. in 24 male patients of similar clinical category treated during 1956. 23 of these were discharged from hospital after an average stay of 23½ weeks—12 returning to full employment, and the other 11 being able to live at home but unable to earn their living. Four of the latter subsequently relapsed. The average stay in hospital of those treated by trifluoperazine and discharged was 12½ weeks. The percentage of patients returned to full employment has been higher in the trifluoperazine group. Trifluoperazine would appear to be a cheaper and more pleasant method of treating acute paranoid schizophrenia than I.C.T., and just as effective, if not more so. A matter of some importance is how long patients should be kept on a maintenance dose. We are not in a position to say how many of these patients would have made a spontaneous recovery from acute attack, or how many are continuing to receive the drug unnecessarily if the attack has run its natural course. We have not taken any risks, but the matter is one that needs further study. We have, as yet, no evidence that the drug, if taken continuously, leads to complications. Of the three cases that proceeded to I.C.T., one made a complete recovery and the other two showed only moderate improvement. These later completely recovered with another course of trifluoperazine.

Summary

Thirty patients suffering from chronic paranoid schizophrenia and twenty from a first attack of paranoid schizophrenia were treated with trifluoperazine dihydrochloride. The results are shown in the capacity for social living before and after treatment, and the effect on different aspects of symptomatology is discussed.

Reference is made to a comparison of trifluoperazine and insulin coma treatment in acute paranoid schizophrenia.

Trifluoperazine should prove a valuable addition to the drugs available for the treatment of schizophrenia.

We are indebted to Smith Kline and French Laboratories Ltd. for the supply of the drug and for the helpful advice in carrying out the experiment.

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ACCIDENTAL HAEMORRHAGE TREATED BY CAESAREAN SECTION*

BY

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The purpose of this review of cases of accidental (retroplacental) haemorrhage occurring at Oldham General Hospital (1953–7) and at Ashton-under-Lyne General Hospital (1953–6) is to emphasize certain clinical aspects of the disease, and to draw attention to the improved foetal survival which can be obtained by the use of caesarean section in a limited group of cases.

The cases under consideration are restricted to those of accidental haemorrhage with retroplacental bleeding, as actually demonstrated at delivery by the presence of a retroplacental clot of whatever size. Cases in which the haemorrhage was entirely revealed have been excluded, likewise placenta praevia.

The hospitals at which these cases have been treated are situated in adjacent areas on the periphery of Manchester, and together serve an industrial population of about 500,000 people. For this reason, and because the methods of assessment and treatment at each centre are identical, the data are presented as a whole.

Material

Incidence.—Over the five-year period in question, 12,657 patients were delivered in the two hospitals, with 466 stillbirths (36 per thousand deliveries) and 325 neonatal deaths (25 per thousand deliveries). There were 92 cases of accidental haemorrhage (less than 1% of the total deliveries)—37 live births, 52 stillbirths, and 3 deaths in the neonatal period. There were no maternal deaths. Cases admitted as emergencies were twice as many as booked cases, but the results were approximately the same for both classes (Table I). Retroplacental haemorrhage associated with delay in or failure of the blood-clotting mechanism and afibrinogenaemia was seen in only two cases, and the combination is considered to be rare.

Clinical Groups.—The cases fell into three groups (Table II). It should be noted that while the most common type of case is the classical concealed or mixed haemorrhage with shock and intrauterine foetal death, there is also a large group of cases presenting with clear-cut evidence of concealed or mixed haemorrhage in which shock is absent or minimal and in which the foetal heart sounds are present on admission to hospital. This group has to be distinguished from yet a third type of case which does not present as one of accidental haemorrhage at all; in these cases the only evidence of placental separation is the presence of a small adherent retroplacental clot when the placenta is examined after delivery; and vaginal bleeding, if it occurs at all, may be so slight that its significance is not appreciated. Careful observation of the foetal heart rate in labour may reveal distress at some stage, however, and in general these cases are treated as cases of foetal distress, the reason for which is not apparent until after delivery.

Toxaemia of Pregnancy.—The standard of toxaemia adopted was a rise of blood pressure to 140/90 alone or in combination with albuminuria and/or oedema. The incidence of toxaemia was 48% and the foetal mortality only slightly higher than in the non-toxaemic cases (Table III).

Age and Parity.—The fact that pregnancies of low parity are much commoner than those of high parity, and that a higher incidence of pregnancy occurs in patients under 30 than in those over 30 years of age, is reflected in the incidence of retroplacental haemorrhage (Table IV): 77% of all the cases occurred in the first, second, or third pregnancies taken as a group, and 63% of all cases occurred in patients under 30 years of age.

The *method of delivery* is summarized in Table V. 76 cases were delivered by the vaginal route and 16 cases by caesarean section.

TABLE I

	Total	Live Births		Stillbirths		Neonatal Deaths	
		No.	%	No.	%	No.	%
Booked ..	32	14	44	16	50	2	6
Emergency ..	60	23	38	36	60	1	2
Total	92	37	40	52	56	3	3

TABLE II.—*Clinical Groups*

Group	Groups	Cases	Incidence
1	Frank retroplacental haemorrhage with shock and intrauterine death	36	39%
2	Frank retroplacental haemorrhage with little or no shock and foetal heart sounds present on admission	31	34%
3	Foetal distress in labour; small retroplacental clot found at delivery	25	27%

TABLE III.—*Toxaemia and Accidental Haemorrhage*

	Total	Incidence	Live Births	Stillbirths	Neonatal Deaths	Foetal Mortality
Toxaemic ..	45	49%	15	29	1	66%
Non-toxaemic	47	51%	22	23	2	53%

TABLE IV.—*Age and Parity in Accidental Haemorrhage*

Age	Total	Parity						Parity Not Recorded
		0	1	2	3	4	5	
Under 30 ..	58	31	22	18	5	10	5	1
Over 30 ..	34							
Total ..	92	71			20			1

TABLE V.—*Method of Delivery*

	Cases	Live Births	Stillbirths	Neonatal Deaths	Foetal Mortality
Caesarean section	16	11	3	2	31%
Vaginal delivery ..	76	26	49	1	66%

Discussion

The accepted method of delivery in concealed or mixed accidental haemorrhage is that of vaginal delivery following artificial rupture of the membranes, preceded by resuscitation in those cases where shock is a feature. This was the method of treatment in 76 cases, in which there were 26 live births and a foetal mortality of 66% (Table V). Of the 49 stillbirths in this group, intrauterine foetal death had already occurred in 36 cases on admission to hospital. In a further 13 cases the foetal heart sounds were present on admission, but intrauterine death occurred before vaginal delivery was accomplished. One of these, however, was a case of

*Paper read at a discussion on accidental haemorrhage held jointly by the Glasgow Obstetrical and North of England Obstetrical and Gynaecological Societies in Glasgow on May 2, 1958.

foetal distress without evidence of accidental haemorrhage before delivery (group 3, Table II), and, if we exclude this case, of 15 cases of frank retroplacental bleeding in which the foetal heart sounds were present on admission, only two infants survived and the perinatal mortality was 87% (Table VI). On the other hand, in

TABLE VI.—*Method of Delivery: Frank Retroplacental Haemorrhage, Foetal Heart Sounds Present on Admission (Group 2, Table II)*

	Cases	Live Births	Stillbirths	Neonatal Deaths	Foetal Mortality
Caesarean section	16	11	3	2	31%
Vaginal delivery . .	15	2	12	1	87%

16 cases where the foetal heart sounds were present on admission and immediate caesarean section was carried out, there were 11 live births and a foetal mortality of only 31%.

These figures, though small, suggest that the perinatal mortality can be improved by the use of immediate caesarean section in those cases in which the foetal heart sounds are present at the time of admission to hospital, and with the minimum of delay where resuscitation is necessary for reasons of shock. The onset of uterine contractions, whether spontaneous or provoked by treatment, is highly undesirable in such cases, since the foetal oxygen saturation—already prejudiced by placental separation—is likely to be further decreased and foetal asphyxia produced by the reduction of bloodflow at the placental site, which will be caused by these contractions.

There appears to be a difference of approach and emphasis in the writings of recent authors on the method of delivery in accidental haemorrhage, with reference to this group of cases. Some adopt a primarily conservative approach, in which vaginal delivery is the method of election (Eadie and Randall, 1954; Barry *et al.*, 1955), and caesarean section is reserved for those cases in which the uterus fails to contract after rupture of the membranes, or in which further retroplacental bleeding occurs, rather than as a means of obtaining a living infant when foetal heart sounds are audible. Tatum (1953) places accidental haemorrhage "associated with toxaemia" amongst his criteria for delivery by caesarean section, and a significant reduction in foetal mortality by the use of caesarean section was reported by Page *et al.* (1954). No uniform opinion is to be found in the standard textbooks: the authors of *Queen Charlotte's Textbook of Obstetrics* (1956) state that "evidence of foetal distress would occasionally justify caesarean section" in mild cases; and Greenhill (1955) prefers vaginal delivery as the method of election, reserving caesarean section for cases complicated by severe toxaemia, or in order to control haemorrhage. On the other hand Brews (1955b) advocates immediate caesarean section for cases where shock is mild and the foetal heart sounds are present. This view is also put forward by Browne and Browne (1955), who state that "caesarean section has a definite though limited place in treatment . . . a distressed foetal heart may be heard when lower segment section should be undertaken without hesitation."

A criticism of caesarean section might be made that, in the last analysis, perinatal deaths are transferred from the stillbirth column to that of neonatal deaths. This, however, has not been so in the small number of cases reported here. Moreover, it is not necessarily an argument against the delivery of a living child by caesarean section with some prospect of survival that a very much greater risk of a stillbirth accompanies vaginal delivery.

A further interesting feature of the different series of cases reported in recent years is the varying incidence of toxaemia. In Eadie and Randall's (1954) series the incidence was only 24%, and in the series here reported the incidence is 48%. Greenhill (1955) quotes the incidence of toxaemia in Dieckmann's series as 69%, and 42% is attributed to Sexton's series at Boston. Brews (1955a) states that some degree of albuminuria is present in 80% of cases, in the majority of which there is evidence of pregnancy toxaemia, essential hypertension, or chronic nephritis; though albuminuria may be explained by shock alone in some cases.

The wide disparity between the reported incidence of toxaemia in the different series quoted may be accounted for by varying standards of definition of toxaemia, but it seems clear that a higher proportion of cases than has hitherto been recognized occurs without any evidence of hypertension or albuminuria at any stage of the disease.

No deductions have been made from the data of age and parity, other than to point out that these figures may be biased by the increased numbers of patients normally occurring in the age group under 30, and by the influence of voluntary family limitation on parity.

Summary and Conclusions

A series of 92 cases of accidental (retroplacental) haemorrhage occurring at Oldham (1953–7) and Ashton-under-Lyne (1953–6) is surveyed.

The incidence of toxaemia, the age and parity, and the method of delivery are discussed.

An analysis of the method of delivery suggests that the best method of delivery for those cases in which the foetal heart sounds are present on admission to hospital is by caesarean section, and this procedure is strongly advocated. The incidence of toxaemia in accidental haemorrhage is very variable, possibly because of varying standards employed in the definition of toxaemia. There is a large group of cases presenting an identical clinical picture in which hypertension and/or albuminuria does not occur, and in which there is no warning whatsoever of the danger of placental separation.

I am indebted to Dr. E. A. Gerrard for many helpful comments; to Dr. A. S. Simpson, Divisional Medical Officer of Health, Ashton-under-Lyne, for statistical advice; and to my colleagues in the Maternity Departments of the Oldham General and Ashton-under-Lyne General Hospitals for allowing me access to cases under their care.

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ABO BLOOD GROUPS AND SEX RATIO AT BIRTH

BY

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"Though I have very little evidence on this head, analogy would lead one to the belief that the tendency to produce either sex would be inherited."—Darwin, *The Descent of Man and Selection in Relation to Sex.*

Sex Ratio at Birth according to the ABO Blood Group of Mothers

In 1925 Hirszfeld and Zborowski pointed out that in their series of 264 white newborn baby–mother combinations the sex ratio—that is, the ratio of males to females—was very much higher for the babies of AB mothers than for the rest—namely, 2.87 (23 : 8) compared with 1.04 (119 : 114)—and they declared that "*if this finding were confirmed it would have far-reaching theoretical significance.*" (Italics mine.) The finding, however, at once fell into oblivion, and it did not appear in any of the invaluable scholarly source-books of Snyder (1929), Lattes (1929), Steffan (1932), and Wiener (1935), or in any of the extensive surveys of early blood group findings by Levine (1928), Witebsky (1932), and Holzer (1935). On its eventual re-emergence Allan (1955) showed that the finding was not confirmed in the aggregate of all the other series of white newborn babies reported in 1924–54, and the same proved true of Cohen and Glass's (1956) large series. In both of the latest (and much the biggest) series, however—namely, the first 5,612 cases of Allan (1958) and the first 15,475 cases of Shield *et al.* (1958), the latter especially—the sex ratio is much the highest for the babies of AB mothers, while *in the aggregate of all the 1924–58 white series the sex ratio of the babies of AB mothers is significantly higher than that of the rest*—namely, 1.26 (667 : 531) compared with 1.08 (16,130 : 14,982). The 1924–56 and 1958 aggregates are shown in Table I.

TABLE I.—*Sex Ratio of White Newborn Babies*

1924–56 White Series				1958 White Series			
Mothers' Group	Male Babies	Female Babies	M./F. Babies	Mothers' Group	Male Babies	Female Babies	M./F. Babies
AB	257	229	1·12	AB	410	302	1·36
O	2,435	2,356	1·03	O	5,231	4,709	1·11
A	2,296	2,279	1·01	A	4,299	3,898	1·10
B	732	639	1·15	B	1,137	1,101	1·03

Non-white Series.—In the aggregate of the only two non-white series reported so far—those of Sanghvi (1951) and of Cohen and Glass (1956)—the sex ratio of the babies of AB mothers is 1.30 (78 : 60), while that of the rest is 1.10 (1,129 : 1,024).

Sex Ratio at Birth when Mothers' and Babies' ABO Groups are the Same

As a result of the oblivion into which Hirszfeld and Zborowski's 1925 observation immediately fell, more than a quarter of a century elapsed before the subject as a whole was brought to life again—"the years that the locust has eaten," as Fraser Roberts (1957) has described the three decades between the papers of Buchanan and Higley (1921) and Aird *et al.* (1953) on the blood groups and disease. This renascence came in 1951, with Sanghvi's finding that in both his series the sex ratio of the O babies of O mothers was significantly higher than that of the A babies of A mothers, and it is notable that a trend in the same direction, to a greater or less degree, is found in each of the individual 1924–58 series, including Dossena's (1924), apart from the five small early white series shown in italics in Table II (cf. Edwards, 1957). Indeed, *in the aggregate of all the 1924–58 white series the sex ratio of the O babies of O mothers is very significantly higher than that of the A babies of A mothers*—namely, 1.11 (5,335 : 4,806) compared with 1.02 (4,054 : 3,972).

TABLE II.—*Sex Ratio of Newborn Babies*, 1924–58

Series in Order of Publication	Total No. of Babies	O Babies of O Mothers	A Babies of A Mothers
Dossena (1924)	148	1·09	0·60
Hirszfeld and Zborowski (1925)	*264*	*0·84*	*1·15*
Badino (1927)	*200*	*0·92*	*2·33*
Klaften (1927)	*200*	*0·67*	*0·90*
Graff and Werkgartner (1928)	*494*	*0·91*	*1·03*
Grünfeld and Schmundak (1928)	168	2·37	1·20
Kirwan-Taylor (1930)	*250*	*1·05*	*1·17*
Goroncy (1930)	285	1·09	0·76
Haselhorst (1930)	2,331	1·07	0·96
Hurst *et al.* (1946)	181	1·07	0·65
Sanghvi (1951)	864	1·29	0·84
Johnstone (1954)	2,429	1·04	1·00
Cohen and Glass (1956)	3,577	1·03	0·93
Shield *et al.* (1958)	15,475	1·16	1·07
Allan (1958)	5,612	1·09	1·00
Sanghvi* (1951)	1,330	1·53	0·99
Cohen and Glass (1956)*	961	1·14	0·74

* Non-white.

Non-white Series.—In the aggregate of the two non-white series the sex ratio of the O babies of O mothers is 1.30 (332 : 255), while that of the A babies of A mothers is 0.87 (183 : 210), the difference being significant.

Sex Ratio at Birth according to the ABO Blood Group of Babies

In the aggregate of the 1924–54 white series (Allan, 1955) the descending order of sex ratios of the babies was shown to be B babies—O babies—A babies, especially where the babies were of the same group as their mothers. This B—O—A descending order appeared yet again in Cohen and Glass's (1956) large series, while in particular the sex ratio of the B babies is, in the 1924–56 aggregate, significantly higher than that of the O babies. In both of the large 1958 series, however, the sex ratio of the B babies is *lower* than that of the O babies, and if this were confirmed the significantly high sex ratio of the 1924–56 B babies might be thought to have arisen from one or other of at least three possible causes. These are: (1) chance variation; (2) some change, however caused, in the selective characteristics of the B gene; and (3) provided the high sex ratio of the 1958 AB babies were also confirmed, the systematic tendency for A_2B individuals, babies especially, to be included among the B's. (The last is a very unlikely cause, owing to the smallness of the number of A_2B compared with B babies.) Meantime it may be noted that *in the aggregate of all the 1924–58 white series the sex ratio of the O babies*

TABLE III.—*Sex Ratio of White Newborn Babies*, 1924–58

1924–56 White Series				1958 White Series			
Babies' Group	Male Babies	Female Babies	M./F. Babies	Babies' Group	Male Babies	Female Babies	M./F. Babies
B	786	656	1·20	B	1,170	1,069	1·09
AB	211	199	1·06	AB	357	283	1·26
O	2,483	2,367	1·05	O	5,431	4,781	1·14
A	2,240	2,281	0·98	A	4,119	3,877	1·06

as a whole is very significantly higher than that of the A babies as a whole—namely, 1.11 (7,914:7,148) compared with 1.03 (6,359:6,158). It is also worthy of note that there is a very significant shortage of A male babies compared with A mothers of male babies—namely, 6,359 compared with 6,595. The 1924–56 and 1958 white aggregates are shown in Table III.

Non-white Series.—In the aggregate of the two non-white series the sex ratio of the O babies as a whole is 1.20 (499:416), while that of the A babies as a whole is 0.93 (332:356)—a non-significant difference. Here, however, there are 332 A male babies compared with 326 A mothers of male babies.

Statistical Note by W. Brass

For all four ABO blood groups combined the sex ratios do not differ significantly as between individual series, and aggregation does not introduce any appreciable bias. It also seems fair to assume that the method of selection of babies did not introduce any dependence of sex on blood group. Thus the significance of differences in sex ratios has been tested by simple contingency table procedures. Three small white series with incomplete data—those of Koller (1926), Grünfeld and Schmundak (1928), and Wolff and Jonsson (1935)—have been excluded from all the totals.

Conclusion

All known series of blood-grouped newborn babies and their parents are combined and analysed in respect of sex ratio, and three main observations are made. (1) In accordance with Hirszfeld and Zborowski's finding, the sex ratio of the babies of white group AB mothers is, in the aggregate, significantly higher than that of the babies of O, A, and B mothers combined. (2) In accordance with Sanghvi's finding, the sex ratio of the white O babies of O mothers is, in the aggregate, very significantly higher than that of the A babies of A mothers. (3) The sex ratio of the white O babies as a whole is, in the aggregate, very significantly higher than that of the A babies as a whole. From these observations it may be concluded that the existence of blood-group differences in the human sex ratio at birth is now a very strong probability, at any rate in the white races.

APPENDIX

Sex Ratio at Birth According to the ABO Blood Group of Fathers

In 1954 Johnstone noted that in his white series of 2,141 baby–father–mother combinations the sex ratio of the babies of B fathers was much lower than that of the babies of B mothers. In view of this it is notable that in the aggregate of all seven white series of newborn baby–father combinations—the other six are those of Dossena (1924), Klaften (1927), Graff and Werkgartner (1928), Kirwan-Taylor (1930), Haselhorst (1930), and Cohen and Glass (1956)—the sex ratios are, in descending order, 1.22 (144:118) for babies of *AB fathers*, 1.09 (1,545:1,423) for babies of *O fathers*, 1.02 (1,506:1,472) for babies of *A fathers*, and only 0.95 (562:594) for babies of *B fathers*. None of these intergroup differences, however, is significant.

My own series is part of a research programme supported by a grant from the Scottish Hospital Endowments Research Trust and the Scottish National Blood Transfusion Association, to whom my grateful thanks are expressed. I am grateful to Professor John Cruickshank and Dr. J. S. Campbell, respectively the past and present Regional Directors of the North-east Scotland Blood Transfusion Service, for much encouragement and help; to Professor Dugald Baird and the nursing and secretarial staff of the Aberdeen Maternity Hospital and its associated nursing homes for their kind co-operation; to Mr. Alfred Johnston and Mrs. Rosaleen Noble for their conscientious technical and secretarial work; and to Mr. William Brass for his statistical analysis of the data, and for much very helpful comment.

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SPONTANEOUS THROMBOSIS OF THE EXTERNAL CAROTID ARTERY

BY

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With the modern widespread use of angiography, thrombosis of the carotid artery tree has been increasingly reported in recent years (Johnson and Walker, 1951; Webster, Gurdjian, and Martin, 1956). This interest has been further augmented by the intervention of surgery in the prevention and reversal of some of the disastrous neurological effects (Eastcott, Pickering, and Rob, 1954; Edwards and Rob, 1956; Hamlin, Sweet, and Lougheed, 1958). All these cases deal with thrombosis of the common carotid and internal carotid arteries. We report here a case of spontaneous thrombosis of the external carotid artery.

Case Report

A man aged 65, a gatekeeper with British Railways, experienced a sudden severe pain on the right side of his head which came on within seconds and lasted with

diminishing severity for 48 hours. Simultaneously with this he experienced numbness and tingling of the right side of his face which also gradually subsided. There were no symptoms below his neck. He was seen by one of us (J. L.), who found extreme tenderness on pressing over the bifurcation of the common carotid artery, and an absence

FIG. 1.—Angiography via right common carotid artery: no filling of external carotid artery.

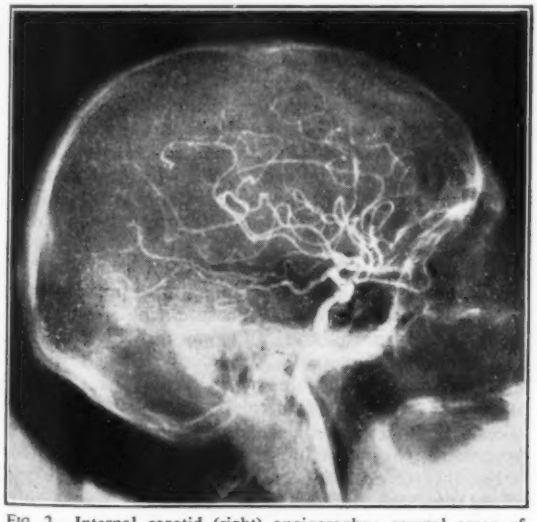

FIG. 2.—Internal carotid (right) angiography: several areas of narrowing and irregularity are apparent.

of pulsation in the temporal and facial branches. He concluded that thrombosis of the external carotid artery had occurred, and asked for an arteriogram to be performed. The patient was admitted to the Churchill Hospital for this purpose under the care of Dr. W. Ritchie Russell on June 2, 1958.

At this time (eight weeks after the event) the patient complained only of occasional discomfort in the right side of the head which would last for about an hour at a time. Apart from the history of severe pain eight weeks previously there was nothing of note in his past history.

Examination revealed a man of poor intelligence but healthy appearance. There were no abnormal physical signs apart from the marked atheromatous changes in the retinal arteries. His blood pressure was recorded as varying from 190/100 to 160/95 mm. Hg. On the left side the pulsation of the common, internal, and external carotid arteries was easily palpable and seemed to be normal. On the right side pulsation of the common carotid artery appeared to cease at the level of a bifurcation, and only on careful palpation could the internal carotid pulsation be felt. Faint pulsation in the palpable branches of the external carotid in the face could be felt, presumably from the development of collateral circulation.

Investigations showed a cerebrospinal fluid protein of 55 mg./100 ml., no cells, a normal Lange test, and negative Wassermann and Kahn reactions. The blood Wassermann and Kahn reactions were also negative. Blood examination gave a haemoglobin of 92% (13.6 g. per 100 ml.), white cells 8,200 per c.mm., and E.S.R. 12 mm. in one hour (Westergren). A skull *x*-ray film showed no lesion and the chest film only emphysematous lung fields.

A right common carotid angiogram revealed a complete occlusion of the external carotid artery (Fig. 1). The internal carotid was patent but narrowed and irregular, both at its commencement and especially in the siphon region (Fig. 2).

Comment

There seems to be little doubt that in this case the sudden onset of right-sided pain in the head and numbness of the face coincided with the occurrence of spontaneous thrombosis of the external carotid artery. We have been unable to find any reference to a similar case, and hence it is of interest to report that this condition should be added to the considerable list of those which may cause pain on one side of the face and head. It seems to be unlikely, however, that this lesion would cause the pain reported in this case were the vascular system quite healthy. The collateral circulation is usually so adequate that symptoms are not expected after external carotid ligation: indeed, this is practised as a treatment for severe epistaxis (Kuhn and Hallberg, 1955; Wolferman and Dwyer, 1955).

We are indebted to Dr. W. Ritchie Russell for advice regarding this presentation and to Dr. P. W. E. Sheldon for carrying out the arteriographic examinations.

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A unique collection of Cambridge treasures will be exhibited at Goldsmiths' Hall, London, from March 17 to April 18. Exhibits of scientific interest include the sixteenth-century silver sceptre of Dr. Caius, co-founder of Caius College, which he originally gave to the College of Physicians when he was its president; apparatus used by J. J. Thomson and Lord Rutherford; a photograph of research students at the Cavendish Laboratory in 1932, which includes most of the world's leading physicists; and the manuscripts of Newton's *Principia Mathematica* and Darwin's *Origin of Species*. Plate, books and manuscripts, paintings and drawings, sculpture, and an extensive range of both serious and amusing historical material will also be shown.

TREATMENT OF HYPERTENSION WITH "MIO-PRESSIN"

BY

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Numerous compounds have been discovered which affect transmission in the sympathetic division of the autonomic nervous system. Most, if not all, of these compounds have been used in the treatment of hypertension with varying degrees of success. The history of treatment has a ring about it which is familiar to most physicians. The patient is given treatment with a new drug as recommended by the manufacturers and after a variable period of time his diastolic pressure falls, often to within normal limits. But with the passage of time it starts to rise again. Increased dosage of the drug may hold it in check for a while, but eventually the dose reached produces limiting side-effects, after which the diastolic pressure slowly but surely returns to the pre-treatment level or even higher.

Fortunately for most hypertensives the blood pressure usually responds again to a change of treatment. It is also becoming recognized that combination therapy is more effective than single drugs. Combination therapy, however, has some drawbacks for both doctor and patient. It can be very time-consuming in a busy clinic trying to reason out which of three components of a treatment should be increased or reduced, and in my experience it is quite beyond the ability of some patients to take different doses of three sorts of pill three or four times a day.

A combination product, "mio-pressin," has recently been introduced which contains the centrally acting agents rauwolfia and protoveratrine together with the long-acting peripheral agent "dibenyline," now generally recognized as the most specific adrenomotor antagonist. This product has been tested in a controlled trial in hospital and the patients have been reviewed for at least 12 months.

Method

Trials of hypotensive drugs are notoriously tricky. Diurnal changes of blood pressure vary over quite wide limits. So do readings on the same patient taken by different members of the staff. A patient with a labile hypertension is often affected by a change of surroundings.

All the patients in this trial had three days' rest in bed without treatment after admission to hospital. During this period and subsequently the blood pressure was recorded at the same time in the morning and evening. The lowest blood pressure during the rest period was taken as the reference points.

The patients were arbitrarily divided into two groups and were treated with coded capsules for a period of 10 days. Treatment was started with one capsule three times daily and increased at three-day intervals until there was a satisfactory fall in blood pressure or the end of the 10-day period was reached. The blood pressure was taken as the mean of the last three readings —that is, the evening reading on the ninth day and the morning and evening readings on the tenth day. At this point patients who had been on placebo therapy were transferred to known active mio-pressin and the dose built up gradually until a satisfactory result was obtained. The patients were discharged from hospital on this dose as maintenance therapy and were seen at regular intervals in a special out-patient clinic.

Each mio-pressin capsule contained 25 mg. of rauwolfia, 0.2 mg. of protoveratrine, and 5 mg. of dibenyline. The placebo capsules contained lactose.

Results

It is the raised diastolic pressure which produces the main strain on the cardiovascular system of the hypertensive patient. The diastolic pressure has been used as the parameter for observation in this investigation. Readings were taken to the nearest 5 mm. of mercury with a standard sphygmomanometer. Readings in the ward were taken with the patient in a sitting position; at review, they were taken with the patient sitting and standing.

All the readings quoted below are in millimetres of mercury.

In-patients.—There were 24 patients (9 males and 15 females) in the group started on placebo treatment. Their ages ranged from 45 to 71 years. After bed rest the mean diastolic pressure was 122 (range 110–140). After further bed rest and treatment with inert capsules the mean fall in diastolic pressure was 7 mm.; after treatment with mio-pressin the mean fall was 27 mm. There were 28 patients (8 males and 20 females) in the group which started on active treatment. Their ages ranged from 36 to 79 years. After bed rest the mean diastolic pressure was 125 (range 110–150). After treatment with mio-pressin the mean fall was 29 mm.

Out-patients.—All patients have now been reviewed over a period of at least 12 months, extending in eight cases to two and a half years. Thirty patients had a lower diastolic pressure at their last review than when they left hospital; 14 had the same pressure; 8 had a higher pressure. Of the eight with raised pressure only two had returned to the pre-treatment level. Twenty-six patients are being maintained on a dose lower than that on which they left hospital; 24 are on the same dose; and the 2 patients quoted above whose blood pressure returned to pre-treatment level had their dose increased. The maintenance dose varies widely and ranges from 1 capsule daily to 2 capsules four times a day. The doses most commonly used are 1 capsule three times a day and 2 capsules twice a day.

Statistical Check

Measurements of diastolic blood pressure can only be approximate. Individual measurements are given to the nearest 5-mm. interval and may well be subject to an error of one interval. The more refined statistical tests are of doubtful value when dealing with data of this type. A χ^2 test may be made by adopting arbitrary criteria of improvement, but the literature on hypertension is inconclusive on what these should be. It has therefore been decided to apply the simple test of relating the difference of the means to its own standard error. Three comparisons are possible: (1) *Placebo-starting group on placebo against the same group on mio-pressin*:—The average fall of diastolic pressure on placebo was 7 mm. and on mio-pressin 27 mm. The difference is 20 mm. and its standard error 3.0 mm. (2) *Placebo-starting group on placebo against the mio-pressin group*:—The average fall on diastolic pressure of the mio-pressin group was 29 mm. The difference is 22 mm. and its standard error 3.9 mm. (3) *Placebo-starting group on mio-pressin against the mio-pressin group*:—The difference here is 2 mm. and its standard error 4.1 mm.

The following conclusions may be drawn from these tests: (1) there is a significant difference between the

fall in diastolic pressure in patients on placebo treatment and the same patients on mio-pressin treatment; (2) there is a significant difference between the fall in diastolic pressure in patients on placebo treatment and a different group of patients on mio-pressin treatment; and (3) there is no significant difference between the fall in diastolic pressure in the two groups of patients on mio-pressin treatment.

Discussion

It is not surprising that a combination of hypotensive drugs produced a satisfactory initial fall in diastolic pressure or that treatment with active material was significantly better than treatment with inert material. It would have been more remarkable if the results had been otherwise.

The most interesting observations from this trial would appear to be those on the out-patients. Of the 52 patients treated, 44 maintained their blood pressure at the lowered level or even further reduced it. In no instance was it necessary to increase the dose of mio-pressin, and in 26 patients the daily dose has been greatly reduced from the original level.

Side-effects were negligible and there was no postural hypotension. One patient complained of dizziness, one of anorexia, and one of blurred vision, but these disappeared without alteration of the treatment.

Summary

Mio-pressin, a combination of rauwolfia, proto-veratrine, and dibenyline, has been used in a controlled trial in hospital. Out-patient reviews have been made over periods from one to two and a half years.

In the controlled trial there was a satisfactory fall in diastolic pressure on active treatment and a significant difference between the results of active and inert treatment.

Of the 52 patients, 44 maintained or reduced the lowered blood pressure. None had the dose of mio-pressin increased, and 26 have had the maintenance dose reduced.

DOES SERUM GONADOTROPHIN CURE ACNE VULGARIS?

BY

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Acne vulgaris starts at puberty and ends in late adolescence or early adult life. This close connexion with the major period of hormonal imbalance has been recognized by the lay public as well as the medical profession for a very long time. Even to-day many doctors use the old cliché, "It's your age; you'll grow out of it," as an excuse for treating acne sufferers lightly, and this mentality has so affected the general public that large numbers of young people suffer agonies of embarrassment in the belief that nothing can be done, and a regrettably high proportion end up with severe scarring of the face, chest, and back.

What, then, can be done for these patients? As most of them have a very greasy skin, measures to counteract this should be of value, and dietary restrictions should be advised, associated with local degreasing by soap and water, applicatio detergens *N.F.*, or 1% cetrimide lotion. Exfoliation of the hyperkeratosis may be obtained by local applications of sulphur or resorcinol or by weekly erythema doses of ultra-violet light. The control of the pustular element has been made much easier in the past few years by the prolonged administration of antibiotics at low dosage, the results of which were summarized by Cronk *et al.* (1956).

None of these treatments can expect to be curative, but with their prolonged administration the patient can be guaranteed that while the acne is present it will be less cosmetically unpleasant, and ultimately there will be much less scarring than might otherwise have occurred. This is useful for the patient but time-consuming for everybody, and better treatments must still be sought

Theory

The closer investigation into the problem of hormonal imbalance was initiated by Pick (1921); a stream of articles followed this over many years until the work of Hamilton (1941) stimulated dermatologists to use oestrogens. Gradually the inadvisability of prescribing these for the male has been recognized, but there has remained a definite place for their use in women during the second half of the menstrual cycle. This is of most value in those whose acne is predominantly of the comedone type. This satisfactory advance led most people to assume that the androgen/oestrogen ratio was at fault, and that this was a fact of prime importance in the causation of acne. Few dermatologists were rash enough to claim that the administration of hormones could effect a permanent cure, as puberty is a dynamic disequilibrium of all hormones, whose ratio alters far too often to be affected by the physician's ministrations.

In 1950 Aron-Brunetière and Fitoussi widened the scope of the theories about hormones by postulating that the imbalance was a result of the interrelation between androgen, oestrogen, and progesterone in the following ratio: $\frac{\text{androgen} + \text{progesterone}}{\text{oestrogen}}$. Following the work of Vignes (1937) and Jausion *et al.* (1941) they produced evidence to show that the administration of 20–30 mg. of progesterone in two or three doses between the 21st and 25th days of the menstrual cycle aggravated acne. They also claimed that chorionic gonadotrophin did the same thing. From this they postulated that the disequilibrium of the $\frac{A+P}{OE}$ ratio was due to a parallel disequilibrium in the hypothalamopituitary mechanism responsible for the secretion of sex hormones. A series of experiments based on this concept led them to use serum gonadotrophin as a treatment, first by injection (Aron-Brunetière, 1954) and later by oral administration and transmucosal absorption (Aron-Brunetière, 1956). This treatment is claimed to give a 61% cure rate in women and 35% in men, with another 25% in women and 43% in men much improved. Only two brief annotations have appeared in British journals: MacKenna (1957) and Cohen (1957) each claim that about 60% of their cases showed considerable improvement.

Such claims warrant further investigation, most particularly when the word "cure" has slipped into the journals, and, unfortunately, into the literature of a pharmaceutical company.

Method

It is always difficult to decide how to investigate the effects of a new drug, especially when there is some

doubt in the investigator's mind about its possible efficacy. Published claims of "60% considerable improvement in three months," particularly with no reference to a controlled investigation, do not impress a dermatologist with an acne clinic and a pride in the results he already obtains. It was therefore thought unjustifiable to substitute for treatment which had shown some success a form of therapy whose results were problematical. It would also be unethical to prescribe an unproved drug for new patients on their first attendance at the department. For this reason a random group of patients was selected from those who had already been regular attendants at the department for at least three months. These people were able to act as their own controls. In all cases the treatment they had received with more or less satisfaction was continued unaltered, and the trial tablets were given in addition.

The treatment these people had been receiving was all part of the usual routine. The mildest cases were given 1% cetrimide as a degreasing application and a mild exfoliative lotion, usually calamine lotion *B.P.* with 3% sulphur. The more severe cases were also treated once a week with an exfoliative dose of ultra-violet light, while the most severe were in addition given the routine antibiotic treatment (usually tetracycline 250 mg. daily for three weeks out of every four), which both the patients and the department have found to be so useful in diminishing or preventing the severe pustulation.

All these people were then provided with tablets labelled A or B and asked to co-operate in an investigation to test the efficacy of a new drug. The course of treatment was for 12 weeks, and at the end of every four weeks each patient was seen and requested to assess whether the additional treatment had increased the effect of the treatment previously given. The actual course of treatment varied from month to month as recommended by the manufacturers, and the patients took two tablets a day for the first four weeks, one daily for the next four weeks, and then one every alternate day for the rest of the trial. They were also instructed not to swallow the tablets but to allow them to dissolve in the mouth.

The severity of each case was assessed at the start of the course: 1 (mild), 2 (medium), and 3 (severe); and the presence of pustulation, comedones, seborrhoea, and scarring was also noted individually for the face, neck, chest, and back. At intervals of four weeks the patient and the investigator between them decided whether or not there had been an increase in the rate of improvement, and this was noted by + for improvement, 0 for no change, and − for a definite deterioration. At the end of the course an overall assessment was made. With this method it has been possible to assess by a controlled technique the effect of serum gonadotrophin on acne. Throughout the investigation neither the patients nor the doctor knew which tablets contained the drug and which were dummies.

Results

The trial was started on a total of 49 patients (29 male and 20 female), of whom six men and three women failed to complete the course; and in none of the defaulters was this failure due to adverse effects of the drugs. The Table shows that 42.9% of those on tablet A and 42.1% on tablet B thought that the addition of the tablet had enhanced the speed of improvement, while 42.9% on A and 47.4% on B noticed no change in either way. 3 out of 21 (A) and 2 out of 19 (B) suffered a definite deterioration during the three months.

Table of Results

Grade of Severity	Tablet A			Tablet B		
	Improved	No Change	Worse	Improved	No Change	Worse
1	8	5	3	3	6	1
2	1	4	—	5	2	1
3	—	—	—	—	1	—
Total ..	9	9	3	8	9	2
Percentage	42·9	42·9	14·2	42·1	47·4	10·5

There is therefore no evidence at all in this trial that the use of oral serum gonadotrophin has any effect on the course of an acne which is already under treatment, and thus there is no justification for an attempt to treat patients in this way to the exclusion of other methods. This conclusion can be stated dogmatically without even the knowledge of which tablets contained the active ingredient.

It is interesting to note that only two patients complained of side-effects when asked. An 18-year-old youth who left the tablet in his mouth to dissolve overnight was sick nearly every morning for the first three weeks, but the symptoms did not reappear after a few days' rest from the tablets; a 20-year-old woman complained that for the first time in her life periods had become irregular. These complaints did not, however, provide a hint to the dispassionate observer of which tablet contained the serum gonadotrophin, as the patients were on different tablets. It was not until after this article was completed that it was disclosed by the manufacturers that B tablets contained the serum gonadotrophin.

Summary

A controlled investigation was performed to estimate whether the addition of serum gonadotrophin to the treatment of acne vulgaris altered the course of the disease. The course was of 100 units daily for four weeks, 50 units daily for the next four weeks, and 50 units on alternate days for the final four weeks. So far as can be ascertained all patients allowed the tablets to dissolve in the mouth, and so absorbed the drug transmucosally. There is no evidence whatsoever from this trial that the patients derived any benefit from the treatment. The uncontrolled trials reported in France and England have not been confirmed, and acne vulgaris remains a condition for the cure of which there is no known remedy.

My thanks are due to Roussel Laboratories Ltd. for going to a considerable amount of trouble to provide me with the serum gonadotrophin and the dummy tablets; also to the Department of Dermatology, Liverpool United Hospitals, where this work was carried out.

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Medical Memoranda

Asphyxia with Nitrogen

A case of asphyxia with almost pure nitrogen under pressure is reported because of its rarity and because cases of a similar nature are likely to become more frequent as "free" diving with self-contained underwater-breathing apparatus (S.C.U.B.A.) becomes an increasingly popular pastime.

CASE REPORT

A licensed aircraft engineer aged 29, a keen and experienced "free" diver, flew round the world. While at Honolulu airfield he asked an airfield technician to refill his 750-litre cylinder with air to a pressure of 150 atmospheres. The cylinder was painted grey with a black-and-white band at its upper end, and was clearly labelled "AIR" (see photograph). In due course the cylinder was returned to him and he came back to this country with it and the rest of his underwater - breathing apparatus.

The cylinder concerned.

Two weeks later he went "free" diving at the local swimming - baths. After boasting to his friend about his "fresh air from Honolulu" he adjusted his equipment, took a few breaths to test the valves, then entered by the ladder at the deep end—6 ft. (1.8 m.)—breathing through his open circuit apparatus. He remembers striking out from the side of the bath and a moment of realization that something was wrong, before becoming unconscious. He remained underwater for only about 30 seconds before his companion realized he was unconscious.

He was quickly and easily brought to the surface, but difficulty was experienced in lifting him to the side of the bath, and his right forehead was then bruised. He was noticed to be intensely cyanosed, especially in his neck, and his mouth was closed tightly on the mouthpiece of the apparatus. He vomited and defaecated almost at once after removal from the water.

Artificial respiration was begun by Schafer's method, and oxygen was administered shortly afterwards by ambulance attendants, who were quickly on the scene from their ambulance station immediately opposite the public swimming-baths. When seen, about 20 minutes after the accident, his behaviour was very similar to that seen in recovery from nitrous oxide anaesthesia. He was stuporous, but could answer his name, repeating it many times. He repeated, "I have been drowned; I am all right," and burst into laughter.

His temperature was 97° F. (36.1° C.), pulse 108, and B.P. 150/90 mm. Hg. There was a superficial bruise on his right forehead. Subconjunctival haemorrhage had occurred in the lateral aspect of his right eye, and pinhead ecchymoses were seen in his right sclera. The pupils were equal and dilated, and reacted to light. The fundi were normal. His cranial nerves were normal, and the only abnormality evident in his central nervous system was that his reflexes were all brisk.

During the next 12 hours his level of consciousness rose to normal. He vomited two or three times. Subconjunctival haemorrhage was evident in both eyes, such that the whole of the sclerae were suffused with blood. He had diplopia and difficulty in focusing. Otherwise he was well and able to get up to go to the toilet. Thirty-six hours after the accident he was discharged home, where he remained symptom-free. His subconjunctival haemorrhages were still obvious three weeks later but were resolving peripherally.

Subsequent analysis of his "compressed air" cylinder showed that it contained oxygen 0.5%, nitrogen 99.5%, carbon monoxide nil. In fact, his cylinder had, by mistake, been filled with nitrogen at Honolulu.

Nitrogen, used commercially as an inert gas for pressurizing aircraft petrol tanks, is stored in cylinders coloured grey (B.S. Colour No. 30) with a black band lettered with the symbol "N." Air is stored in cylinders of identical grey colour, but with no black band or symbol. Both cylinders have a right-hand screw thread. It is easy to understand how this mistake in identification of cylinders occurred.

To conclude this unusual record of chance occurrences it seems reasonable to report that the patient was tragically killed five weeks after this incident in an air crash in the Libyan Desert.

DISCUSSION

The points of interest and the lessons to be learned from this case are as follows.

1. Nitrogen is present in atmospheric air at about 79%, and is an inert odourless, colourless gas. Sudden exposure to air containing less than 4% of oxygen causes loss of consciousness, with hardly any warning symptoms, within about 40 seconds (Hunter, 1957). Francheteau (1954) describes the rapid onset of unconsciousness occurring in three men who entered atmosphere containing 96% nitrogen, and Wright (1940) states that unconsciousness develops suddenly in 45 seconds if pure nitrogen is inhaled. In the case reported unconsciousness occurred in less than 60 seconds after breathing pure nitrogen. A simple safety precaution can immediately minimize the dangers of a repetition of this accident. It is recommended that all "free" divers using S.C.U.B.A. breathe through their apparatus for a timed 60 seconds, observed by a companion, before they enter the water. If their cylinders are charged with pure nitrogen by mistake they will become unconscious in that time, and their companions will have a relatively easy task reviving them.

2. The accident reported is analogous to the "mistaken cylinder" accidents of anaesthesia, the incidence of which has been reduced by strict care in the identification of cylinders by their colouring and labelling. Commercially, care is taken also, and distinctive colours and left-hand threads are used for the cylinders of potentially explosive gases. Air and nitrogen cylinders, however, are a similar grey colour. A change of nitrogen cylinders from grey to a more distinctive and alarming colour is recommended.

3. It seems reasonable to assess this patient's symptoms and signs as resulting from three factors: sudden unconsciousness due to anoxia; subsequent behaviour due to nitrogen intoxication ("nitrogen narcosis"—Hunter, 1957); and his subconjunctival haemorrhages due to local "squeeze" (Lanphier, 1957), a pressure effect similar to suction produced in his face-mask while he lay unconscious under 6 ft. (1.8 m.) of water.

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Reviews

INSTRUCTION IN GYNAECOLOGY AND OBSTETRICS

Obstetrics and Gynecology. By J. Robert Willson, M.D., Clayton T. Beecham, M.D., Isador Forman, M.D., and Elsie Reid Carrington, M.D. (Pp. 605; illustrated. 80s.) London: Henry Kimpton. 1958.

This book has developed out of a mimeographed summary of lectures given to third- and fourth-year students at Temple University School of Medicine, Philadelphia. It possesses three outstanding features. The first is that no artificial boundary is recognized between obstetrics and gynaecology. This is shown by the following sequence of sections and chapters: dysmenorrhoea and premenstrual tension, endometriosis, fertilization, development, physiology and disorders of the placenta, foetal development, infertility, abortion, ectopic pregnancy, hydatidiform mole, chorion carcinoma, and physiology of normal pregnancy. Further, puerperal infection is considered in the same chapter as acute and chronic gonorrhoea, tuberculosis, and miscellaneous infections. The second feature is the respect for and frequent appeal to physiological facts and principles. Methods for staining vaginal smears to show oestrogenic and progesterone activity are well illustrated, as are those for examining spermatozoa. The third is the unusual balance of the book. Dyspareunia, frigidity, masturbation, the cellular diagnosis of carcinoma, and perinatal mortality are discussed, while pudendal block is treated in detail and well illustrated. The indications for forceps delivery, caesarean section, and breech extraction are also discussed, but no details of these procedures are given. Similarly, no gynaecological operation of any magnitude is described, and neither hysterectomy nor myomectomy is mentioned in the index.

The authors are clearly sound clinicians who require their students to obtain a knowledge of obstetrics and gynaecology which will be useful in general practice. They expect a doctor to undergo further specialized training if he proposes to apply the forceps or extract a breech. This book would not be adequate for a final examination in Britain, but I am probably not alone in thinking that it is more important for the average student to learn how to perform a pudendal block than to extract a breech or perform hysterectomy. It is to be hoped that this pioneering trend will find favour and help in the reorientation of medical instruction.

G. W. THEOBALD.

HEART DISEASE IN THE YOUNG

Heart Disease in Infancy and Childhood. By John D. Keith, M.D., Richard D. Rowe, M.B.(N.Z.), F.R.C.P.(Edin.), and Peter Vlad, M.D. (Pp. 877+xiv; illustrated. £7 17s. 6d.) New York and London: Macmillan Company. 1958.

The writing of any kind of textbook on cardiology at the present time, when progress continues to be so rapid, is no mean task, as anyone who has tried it knows. It is difficult enough when the book is compiled by numerous experts, each responsible for his own section; more so when undertaken by a single team. By the time the last chapter is written the first may be out of date, and the time lag in the press, which is usually considerable with a work of this kind, magnifies the defect. This volume by John Keith and his colleagues at the Hospital for Sick Children, Toronto, illustrates this difficulty in some respects, but on the whole is up to date. It has the great advantage of uniformity, lack of repetition, and proper design; it has a consistent texture and flavour, and reads well; it is a book with a personality.

Since about 88% of the 2,138 cases that provide the material for the authors' experience had congenital heart disease, it is right that nearly three-quarters of the book should be devoted to this subject. There are some helpful chapters on current investigatory techniques, and the last 200 pages or so deal with rheumatic carditis and other diseases or disorders of the heart encountered chiefly in infancy or childhood. Appendices on pre- and post-operative care and on drugs and dosages for infants and children are helpful. But the book will be judged by its major contribution on congenital heart disease. Based as it is on the rare experience of the Toronto group, much will be expected of it—perhaps too much. It is relatively weak on physical diagnosis, and descriptive patterns are not drawn sharply enough. Perhaps this is inevitable in the case of infants, but should not be so with older children. Clinical differential diagnosis might have been tackled in a more disciplined way. Special investigations are described accurately, and the angiocardiograms are outstanding.

The literature is well represented and personal views are not over-emphasized. The tone of the whole work is modest, well balanced, and infinitely careful and sincere. The illustrations are excellent, well chosen, and necessary. What, then, is the matter with it? For there is something wanting. Perhaps it is too subdued, too deferential, too gently phrased. It seems to lack vitality and originality, fails to arouse sufficient curiosity, deals too much with crude facts and too little with reason, fails to throw more light on controversial problems, and will not stimulate research. In a word, it is a little colourless. Nevertheless it is a fine contribution to cardiology and represents enormous labour. It must rank as one of the best in its field, and is highly recommended to all who are engaged on the subject. The authors should be congratulated on their achievement.

PAUL WOOD.

CHILDHOOD TUBERCULOSIS IN U.S.A.

Tuberculosis in White and Negro Children. Volume I. *The Roentgenologic Aspects of the Harriet Lane Study.* By Janet B. Hardy, M.D., C.M. Volume II. *The Epidemiologic Aspects of the Harriet Lane Study.* By Miriam E. Brailey, M.D., Dr.P.H. (Pp. 122+vii and 103; illustrated. Vol. I, 60s.; Vol. II, 36s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1958.

The Harriet Lane Study originated in 1928 in a special out-patient clinic for young children already infected with tuberculosis, and by the standards of those days was a far-seeing venture likely to answer many questions of practical importance at that time, especially the later risks run by children infected early. The results, published 30 years later, and based on clinical records which were closed in 1950, have lost much of their practical importance for communities where anti-tuberculous chemotherapy is readily available; indeed, some of the case histories with their relentless progression, and some of the very high mortality figures, serve mainly to emphasize how greatly prognosis has changed.

Volume I is almost entirely an atlas of radiographs of tuberculosis in children; the quality is reasonably good, but some of the plates appear to have been made from

originals not of the highest quality. There is an error in rib levels in the caption to Fig. 2.

Volume II deals with the prognosis of tuberculous infection in children, and with the risk of such children later developing "reinfection pulmonary tuberculosis." Both emphasize the much higher risk in negro than in white children, largely from similar low-income groups. The risks after infection acquired in the first year or two of life are clearly demonstrated. In the light of recent surveys concerning the development of tuberculosis in children already infected by early teen ages, perhaps the most surprising finding is that only 2 of 434 infected white children are known to have developed phthisis subsequently.

V. H. SPRINGETT.

AIR POLLUTION

Air Pollution: Based on Papers Given at a Conference held at the University of Sheffield, September, 1956. Edited by M. W. Thring, M.A., F.Inst.P., F.Inst.F., M.I.Chem.E. (Pp. 248+x; illustrated. 42s.) London: Butterworths Scientific Publications. 1957.

In 1956 the University of Sheffield organized a course on air pollution, and the component lectures have since been gathered together in a book. The course was held in the Department of Fuel Technology and Chemical Engineering, and it is therefore not surprising to find that Professor John Pemberton, in his lecture on the effects of air pollution on health and vegetation, has had to talk of windpipes and phlegm; no such concessions are made to physicians by the technologists who have contributed many excellent chapters rightly concerned with the prevention of pollution.

A book by 15 authors is apt to be uneven in quality, and this collection of essays would have benefited by more severe editing. Meaning is too often obscured by bad style, and among the abundant illustrations are many which, having probably served well as lantern slides, are intrusive and not wholly appropriate to the text. These irritant blemishes could be due to too much haste in publishing what is really a valuable and authoritative text on technological aspects of air pollution.

P. J. LAWTHER.

REHABILITATION

Rehabilitation after Illness and Accident. Edited by Thomas M. Ling, M.D., M.R.C.P., and C. J. S. O'Malley, C.B.E., M.B. (Pp. 119+vii. 12s. 6d.) London: Baillière, Tindall and Cox. 1958.

In essence, this little book is a plea that more than lip-service be paid to the concept of patients as individual human beings. The physical side of rehabilitation—namely, physical and occupational therapy—is indicated, but the emphasis of the book is on the need to recognize, understand, and deal with patients' hopes and fears and economic and emotional needs. It stresses the importance of recognizing that "rehabilitation" is not something provided because the patient is still not able to return to work after the standard medical or surgical treatment has been completed, but a comprehending and comprehensive approach to all the problems set by illness or by injury from the time of its occurrence. A chapter on organization of rehabilitation and a list of the Ministry of Labour's Resettlement Units are particularly helpful. This book is commended to all who set the care of patients above the treatment of disease.

P. S. LONDON.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Guide to Using the Mill Hill Vocabulary Scale with the Progressive Matrices Scale. Prepared by J. C. Raven, M.Sc. Revised and reprinted. (Pp. 64. 5s. 6d.) London: H. K. Lewis and Co. Ltd. 1958

Lectures on Epilepsy. Edited by A. M. Lorentz de Haas. (Pp. 172+vii. 24s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. London: D. Van Nostrand Co. Ltd. 1958.

Psychiatry in General Practice. By J. A. Weijel, M.D. (Pp. 208+viii. 37s. 6d.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. London: D. Van Nostrand Co. Ltd. 1958.

Principles, Problems, and Practices of Anesthesia for Thoracic Surgery. By Henry K. Beecher, M.D. Revised second printing. (Pp. 74+ix. 27s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Terceiro Curso de Cardiologia. Arritmias. By Eduardo Coelho with the collaboration of A. Bordalo e Sá, António Sousa Borges, Mário Gomes Marques, Eduardo de Paiva, Artur de Oliveira, Salomão Sequerra Amram, Fernando de Pádua, and José Filipe da Costa. (Pp. 319+vi; illustrated.) Lisbon: Imprensa Medica. 1958.

Quarto Curso de Cardiologia. Electro-Vectocardiografia. By Eduardo Coelho with the collaboration of Manual Joaquim Sousa Ventura, A. Sales Luis, Salomão Sequerra Amram, A. Bordalo e Sá, A. Lopes Pimenta, and Fernando de Pádua. (Pp. 380; illustrated.) Lisbon: Imprensa Medica. 1958.

Fractures et Luxations. By Professor P. Mathieu. (Pp. 211; illustrated. 1,500 fr.) Paris: L'Expansion Scientifique Française. 1959.

The Teaching and Learning of Psychotherapy. By Rudolf Ekstein, Ph.D., and Robert S. Wallerstein, M.D. (Pp. 334+xvi. 42s.) London: Imago Publishing Co. Ltd. 1959.

The Pharmacology of Plant Phenolics. Proceedings of a Symposium held at Oxford, April, 1958. Editor J. W. Fairbairn. (Pp. 151; illustrated. 30s.) London, New York: Academic Press. 1959.

Disease and Destiny. Logan Clendening. By Ralph H. Major. (Pp. 49; illustrated. $2.) Lawrence: University of Kansas Press. 1958.

I Tumori del Pancreas Endocrino. Anatomia Patologica e Fisiopatologia Correlativa della Sindrome Ipoglicemica. By A. Piccaluga and M. de Maurizi. (Pp. 173. L. 2,800.) Bologna: Cappelli. 1958.

Poliomyelitis. Papers and Discussions Presented at the Fourth International Poliomyelitis Conference. Compiled and edited for the International Poliomyelitis Congress. (Pp. 684+xviii; illustrated. 60s.) Philadelphia, Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1958.

Treatment in Internal Medicine. By Harold Thomas Hyman, M.D. With a foreword by Walter C. Alvarez, M.D. (Pp. 609+xiv; illustrated. £5.) Philadelphia, Montreal: J. B. Lippincott Co. London: Pitman Medical Publishing Co. Ltd. 1958.

Urology in General Practice. By Frank Coleman Hamm, M.D., M.S., F.A.C.S., and Sidney R. Weinberg, M.D., F.A.C.S. (Pp. 293+vii; illustrated. 48s.) Philadelphia, Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1958.

Mould Fungi and Bronchial Asthma. A Mycological and Clinical Study. By P. J. Van der Werff. Vol. 1. (Pp. 174+xiv; illustrated. 22.80 fl.) Leiden: H. E. Stenfert Kroese N.V. 1958.

Long-term Illness. Management of the Chronically Ill Patient. Edited by Michael G. Wohl, M.D., F.A.C.P., with the collaboration of 79 contributing authorities. (Pp. 748+xix. £5 19s.) Philadelphia, London: W. B. Saunders Company. 1959.

Cardiac Arrest and Resuscitation. By Hugh E. Stephenson, Jr., M.D. (Pp. 378; illustrated. 90s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1958.

Dorland's Pocket Medical Dictionary. Twentieth edition. (31s. 6d.) Philadelphia, London: W. B. Saunders Company. 1959.

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MARROW TRANSPLANTATION AND RADIOTHERAPY OF CANCER

Elsewhere in this issue of the *Journal* Dr. K. A. Newton and his colleagues at the Westminster Hospital describe a new technique in the treatment of cancer which may help to make radiotherapy a more powerful weapon than it already is. Their account of the treatment of two patients who were given infusions of stored autogenous bone marrow after massive doses of irradiation to the entire thorax shows how the results of recent laboratory research are being applied clinically. Their use of tissue transplantation—autogenous transfer—is similar in principle to skin grafting ; but the immediate stimulus for the idea arose from research in homografting. Over the years many methods of transplanting organs and tissues between individuals have been tried and found wanting because the necessary complete basic information was still lacking. Nevertheless, progress is being made, and an encouraging report (see p. 575) comes from Drs. H. E. M. Kay and M. Constandoulakis, of the Royal Marsden Hospital, where a foetal tissue bank has been established, one of the uses of which will be to supply suspensions of haemopoietic cells for the treatment of patients in need of bone-marrow replacement.

Owing in large part to the now classical studies of P. B. Medawar,[1] it is generally agreed that homografts fail to take because of the development of an immunological response by the recipient against the graft. The vehicle of the response is not a soluble antibody but the sensitized cells of the host's lymphoid tissues, which are carried to the site of action, the graft, by the blood stream. This characteristic does allow transplantation to privileged sites where the grafts get no direct blood supply from the host—the cornea, cartilage, and the endometrium for the fertilized ovum. Also permitted is the transfer of tissue which depends not on the survival of the cells of the graft but on the provision of a scaffold into which the host's cells can infiltrate—for instance, bone and artery. And blood transfusion becomes a special example, since the "graft" is not of tissue-cells but of "ghosts"—red corpuscles—which have lost their nuclei and presumably the "nuclear" antigens which stimulate the homograft response.[2] The "nuclear" antigens may well be mucopolysaccharides not unlike the blood-group substances.[3]

According to the present immunological law, therefore, true tissue-transplantation—the replacement of worn-out tissues by living spare parts—depends either on finding a donor whose tissue antigens will not elicit an immune response in the recipient, or on "conditioning" the recipient in such a way that his immunological system will not respond to a selected donor (but will respond to other foreign antigens such as bacteria).

Since there is at present no method for typing the histocompatibility antigens in man, though progress has been made in the mouse,[4 5] the only safe donor to man is his identical twin. J. E. Murray, J. P. Merrill, and J. H. Harrison[6] have had success in transplanting kidneys from donors to their uniovular twins in six out of seven cases. Conditioning the subject to accept tissues from his binovular, non-identical twin can occur in man by exchange in foetal life of haemopoietic cells through a common placental circulation. A number of such natural chimeras have recently been reported in man[7] and sheep[8] ; they have long been known in cattle.[9] Artificial chimeras have been produced in laboratory animals by injection of foreign cells into the foetus[10] or newborn.[11] In all these cases the immunological tolerance of the subject is specific for the antigens of the individual donor: it is as it were the inverse of specific immunity.

A much less subtle method of treating the subject is by blasting him all over with x or γ rays, completely

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[27] Humble, J. G., and Newton, K. A., *Lancet*, 1958, **1**, 142.
[28] Thomas, E. D., Lochte, H. L., Jr., and Ferrebee, J. W., *Blood*, 1959, **14**, 1.
[29] Ferrebee, J. W., *et al.*, *Surgery*, 1958, **43**, 516.
[30] Kurnick, N. B., Montano, A., Gerdes, J. C., and Feder, B. H., *Ann. intern. Med.*, 1958, **49**, 973.
[31] Porter, K. A., and Couch, N. P., *Brit. J. exp. Path.*, 1959, **40**, 52.
[32] *The Times*, February 16, 1959.

destroying his existing lymphoid (and myeloid) cells and thus his capacity to react against foreign antigens. Normally the requisite dose of radiation is lethal. But mice irradiated with lethal doses in this way can recover if injected with normal haemopoietic tissue,[12 13] and it is now known that the recovery is due to the injected haemopoietic cells acting as a graft re-colonizing the myeloid and lymphoid tissues of the host.[14] Once again an artificial chimera has been produced, and since the graft supplies the lymphoid tissue the chimera will take further grafts of other tissues with the same antigens.[15 16] However, a complication has first to be overcome. The maturing lymphoid tissue of the donor can react immunologically against the host's antigens, and this can prove fatal.[17] Experience has shown that this reaction is precluded or minimized by the use of foetal[18 19] rather than adult haemopoietic tissues for inducing chimerism.

The finding that the host's haemopoietic tissue was replaced by the donor's after lethal doses of *x* rays led to the idea that malignant disease might be treated in this way, for it permitted the delivery of a dose of radiation larger than was otherwise tolerable. First attempts by D. W. H. Barnes and J. F. Loutit[20] to treat artificially transmitted mouse-leukaemia showed that even the larger lethal doses of high-intensity *x* rays were insufficient to eliminate all the leukaemic foci. There were suggestions, however, that the immune response of selected foreign, grafted, normal haemopoietic cells could complete the elimination but killed the host too. M. J. De Vries and O. Vos[21] made similar observations. The first application of this method to treat natural leukaemia in the mouse has also been unsuccessful.[22] Later attempts to treat transmitted leukaemia have had limited success,[23] especially when the total dose of *x* rays was increased with concomitant reduction in dose rate.

This prospect of effecting a cure in "incurable" malignant disease has naturally stimulated independently a number of clinicians. Their experiences have been informally reported at meetings of the Blood Club[24] in the U.S.A. Particularly enthusiastic in approach is the group at Cooperstown, N.Y., where J. W. Ferrebee and his colleagues are at work. They had first to surmount a number of preliminary hurdles. Human haemopoietic tissue—adult bone marrow or foetal liver—had to be collected, stored, and, suitably viable, prepared and suspended for intravenous administration. As with whole blood so with marrow, the donor can be "on the hoof," adequate amounts of fresh marrow being obtainable from the sternum and iliac crests. Larger amounts of marrow can be salvaged from cadavers and stored in glycerol at −79° C.[25] like murine tissue.[26] And there seem to be no undesirable immediate reactions from the administration, which may be intravenous or intra-arterial.[27] Preliminary clinical trials with these normal haemopoietic cells to restore the tissues of *x*-irradiated leukaemic subjects have been carried out.[28] A few patients have survived for several months, but there is as yet no unequivocal evidence of a permanent "take" of the donor's cells. As with the irradiated dog given homologous cells,[29] immunological defences against infective agents are impaired. And, until methods can be devised to irradiate the whole subject uniformly and totally, it is unlikely that all leukaemic cells will be sufficiently attacked.

Meanwhile several other groups have made ingenious attempts to treat secondary metastatic neoplasms. Autogenous marrow free of cancer cells has been obtained and stored. The secondary growths in the trunk are then irradiated with what would normally be prohibited doses and the stored marrow is infused intravenously after the radiotherapy. N. B. Kurnick and his colleagues[30] failed to cure either of their two cases, though there were grounds for believing that the autograft did function in one. We have already mentioned the two cases reported in this issue by Dr. Newton and his colleagues. In one of these there was remarkably little general disturbance after supervoltage irradiation of the thorax and infusion of autogenous bone marrow: the mass in the thorax disappeared and has so far not recurred.

At present the question of greatest significance in tissue transplantation is: Will homologous marrow permanently "take" in man as in the mouse or only ephemerally as in the dog?[31] It is to be hoped that evidence will accrue from recent experience in Paris, where, it has been reported,[32] several physicists from Yugoslavia were given infusions of bone marrow as treatment for aplastic anaemia resulting from accidental exposure to an estimated lethal dose of radiation and recovered.

NATURAL HISTORY OF CANCER

A difficulty which frequently arises when assessing any new form of treatment for cancer is the fact that so little is known about the natural history of the disease, in either its preclinical or clinical phases. We are apt to forget that there must be first a preclinical or occult phase before the malignant tumour has caused signs or symptoms or is diagnosable in any way. We know very little of this initial stage, perhaps not even whether it is to be

measured by months or years, and when at length what may be called the clinical phase is reached and the developing tumour begins to give rise to signs or symptoms it is surprising to find how often these seem to be accidental in character. Clinical indications may occur early or late ; as a consequence of this, in some cases a malignant tumour is diagnosed while still localized to its site of origin, whereas in other cases the clinical phase begins only when lymphatic and venous spread has already occurred.

The problem of tracing the natural history of cancer is only partially avoided if we skip the initial preclinical phase of the disease and take as our starting-point the onset of symptoms or date of diagnosis, because from this point onwards the natural course of the disease may be altered by treatment. There remain no doubt a small number of patients who for one reason or another fail to receive any form of treatment which would be expected to influence the progress of the disease, but at all events when the tumours are at accessible sites these untreated patients do not provide a representative sample of cancer as a whole, nor is the fate of untreated cases commonly recorded. In the treated group of patients the centre of interest naturally shifts from the point of view of an observer to that of a partisan, and the main question now is, How effective has the treatment been ? In other words, How much has it altered the expected natural course of the disease ?

This question also is not an easy one to answer, especially in cases treated by radical surgery when the only information available is the five-year survival rate. This simply records the number of patients still living five years after operation. Included among these surgical survivors are some who might have lived five years if they had received no surgical treatment (patients with slowly growing tumours), and others who have survived five years with known recurrences, and again others who, though apparently well on the fifth anniversary of their operation, are destined to succumb subsequently from a reawakening of a dormant metastasis. No doubt a large proportion of five-year survivors owe their lives to surgery, but the inclusion of the other unspecified fractions among the total tends to exaggerate the benefits derived from surgery. On the other hand the five-year survival rate fails to do full justice to surgery because it does not take into account the improvement in general health that so often results from the removal of a primary malignant tumour. For these reasons the full benefit of surgical treatment can never be measured by the arithmetic of statistics, nor for similar reasons is it easy to say exactly how much the natural course of cancer is influenced by surgical treatment.

A further difficulty in the study of the natural history of cancer arises from the astonishing variability in the rate of growth of different tumours even of the same organ of the body. It is a well-established clinical observation that some malignant tumours grow slowly and run a relatively benign course whereas others spread rapidly and soon kill the patient. Study of growth rates has led to the assumption that each tumour, right from its inception, has an individual biological potential, and is predetermined, so to speak, to grow at a certain pace. Histological examination lends some support to this idea, for an undifferentiated or anaplastic tumour grows rapidly, whereas a well-differentiated neoplasm grows more slowly and is less likely to metastasize. This is the underlying principle of the histological grading of tumours, which has proved to be a useful aid to prognosis in tumours of some organs, though not of all.

The doctrine of biological predeterminism is fashionable in some quarters, and those who accept it speak as if the biological potential of a cancer were decided once and for all in the earliest preclinical phase, long before the disease had manifested itself in signs or symptoms. Clinical experience certainly provides much to support the view that constancy of growth is a general characteristic of tumours and that individual tumours usually conform to type ; yet for all that most experienced surgeons can point to glaring exceptions to any general law of this character. Sir Gordon Gordon-Taylor, in his Mitchell Banks Lecture published in this *Journal* last week,[1] provided many striking examples of the unexpectedly long periods for which patients with cancer had survived. He has made an important contribution to the study of the natural history of cancer by collecting together this remarkable series of exceptional cases. They are exceptional in that they do not conform to the general rule, but in scientific inquiries it has often happened that more has come to light by the study of exceptions than by amassing facts about the conforming majority.

It is clear from the evidence Gordon-Taylor has marshalled in his characteristically authoritative yet modest way that cancer does not always sweep on relentlessly to a fatal issue. The fact that some patients come to terms with their malignant tumours, so to say, or even sometimes seem to get the better of them, should inspire us all once more to renew the search for a way of controlling cancer without resorting to radical surgery.

[1] Gordon-Taylor, G., *Brit. med. J.*, 1959, 1, 455.

AN ADVANCE IN CARDIAC SURGERY

In 1957 we published a paper on experimental cardio-pulmonary bypass by a Westminster Hospital team under the direction of C. E. Drew.[1] Members of his team have recently made a new and important advance in this field. By incorporating a new technique of cannulation of the pulmonary artery, the subject's lungs are utilized to oxygenate the blood, and so it is possible to eliminate the machine-oxygenator, which is the main source of serious complications. By means of purely cardiac bypass so produced it is possible to induce deep hypothermia—below 15° C. (59° F.)—by extracorporeal cooling of blood flowing from the left atrium. At this low temperature it is then possible to shut off completely all circulatory flow during the actual repair of the intracardiac defect. Technical details of the development of the method in dogs were given recently by G. Keen.[2]

The left femoral artery is exposed; then, after thoracotomy and the administration of heparin, catheters are inserted into the right and left atria, and a cannula is placed in the left femoral artery. About 20–25% of the left atrial flow is drained into a well, whence it is pumped through a heat exchanger (2–4° C.) and returned to the left femoral artery. The body temperature drops rapidly: when approximately 25° C. (77° F.) is reached the cardiac action becomes impaired and the circulation falls markedly. At this point a small stab wound is made in the upper part of the right ventricle and a catheter is introduced via the pulmonary valve into the pulmonary artery. The right atrial flow (the whole venous return) is then allowed to drain into a second well, whence it is pumped through the lungs via the pulmonary arterial cannula. The left-sided bypass is now fully opened and the rate of the pump is increased. Cooling continues until the body temperature is below 15° C. (59° F.). The pumps are then turned off and artificial respiration discontinued; the venae cavae are closed by tapes, and the heart is drained. Cardiotomy is then performed and the intracardiac defect repaired. On completion of this the action of the heat exchanger is reversed to warm the blood until normal body temperature is approached.

The method has now been used successfully in clinical cases. In one example a child of 4 years underwent successful repair of ventricular and atrial septal defects at a temperature of 15° C. with complete circulatory arrest for 45 minutes; post-operative recovery was uncomplicated. These are remarkable figures and they testify to a notable advance in this field.

[1] Drew, C. E., *et al.*, *Brit. med. J.*, 1957, **2**, 1323.
[2] Keen, G., at Society of Thoracic Surgeons Meeting, November, 1958.

CHEMISTRY AND INSANITY

The idea that some hitherto undiscovered metabolic derangements lie at the root of schizophrenic and manic-depressive illnesses is an old one. In each generation the chemical techniques of the time have been applied by a few brave spirits, and some odd facts turned up which neither explained mental illness nor proved of much practical use, a discouraging terminus. Thus in 1931 P. K. McCowan and J. H. Quastel[1,2] confirmed that patients in depression have an abnormal glucose tolerance curve, which improves as they get mentally better, and recently I. G. Pryce, using an intravenous test, found the same thing.[3] Yet this metabolic abnormality remains unexplained, a subject for endocrinological speculation. Over 20 years ago R. Gjessing[4,5] studied periodic catatonic schizophrenics, in whom he found a cycle of nitrogen retention and excretion associated with the cycle of mental upset. He tried to prevent nitrogen retention with doses of thyroid, and succeeded thereby also in preventing the reappearance of the psychosis. The curative value of thyroid treatment has been confirmed,[6] and the nitrogen retention studied a little further,[7] yet its mechanism remains a mystery and the therapy unused.

Present-day guesses at normal brain function include the idea that certain chemicals or neurohumours present in brain tissue—noradrenaline and serotonin in particular—play an important part in central synaptic transmission. If this were so, such substances and their normal metabolites would be worthy of special study in psychotics. A change in urinary excretion in association with some particular mental phase might point to a metabolic disorder as the basis of the illness, and this could be explored by further experiment. Weil-Malherbe is already well known as one of the pioneers in developing methods of estimating adrenaline and noradrenaline in human urine and blood, and he has now applied[8] his methods to a study of urinary excretion of neurohumours in three patients with periodic attacks of manic-depressive psychosis. Estimations were made on 24-hour specimens of urine at intervals in both manic and depressive phases of the same person, and also on specimens from a group of six depressed and five manic patients who could be compared.

The chief finding was that during manic attacks there was an increase in the urinary noradrenaline (and adrenaline), and also possibly in 5-hydroxyindole acetic acid (5-H.I.A.A.), the chief metabolite of serotonin. In the cases most carefully studied the manic phases also showed higher outputs of urine and sodium; but since the intake of food and fluid was not controlled we cannot be sure that this is a pathological change and not perhaps a consequence of the increased thirst and

[1] McCowan, P. K., and Quastel, J. H., *Lancet*, 1931, **2**, 731.
[2] —— —— *J. ment. Sci.*, 1931, **77**, 525.
[3] Pryce, I. G., ibid., 1958, **104**, 421.
[4] Gjessing, R., *Arch. Psychiat. Nervenkr.*, 1935, **104**, 355.
[5] —— *J. ment. Sci.*, 1938, **84**, 608.
[6] Bonkalo, A., Lovett Doust, J. W., and Stoke, A. B., *Amer. J. Psychiat.*, 1955, **112**, 114.
[7] Gjessing, L., Bernhardsen, A., and Froshang, H., *J. ment. Sci.*, 1958, **104**, 188.
[8] Ström-Olsen, R., and Weil-Malherbe, H., ibid., 1958, **104**, 696.

appetite said sometimes to be present in mania. However, this point will be easy to settle in further work. Likewise the rise in excretion of noradrenaline needs further study before it can be interpreted: does the cerebrospinal fluid contain noradrenaline at this time? Does the patient show clinically signs of sympathetic hyperactivity, for instance? The important first step is that there is a change.

Both chemical pathology and endocrinology have made such strides in the past twenty years that the possibilities of chemical investigation of psychosis are enormous. A type of case particularly suitable for biochemical study is one in which the symptoms have a periodic character, as Dr. J. L. Crammer points out in an article at p. 545 of the *Journal* this week. He believes they are commoner than is generally realized and that more research into them would yield worthwhile knowledge about the causes of psychosis. Unfortunately few mental hospitals have any of the laboratory facilities now taken for granted in general hospitals—a flame photometer for estimation of sodium, potassium, and calcium, for instance, or a good photoelectric colorimeter, or the equipment for nitrogen estimations, let alone the possibility of total 17-hydroxycorticosteroid estimations in urine, or analysis for 5-H.I.A.A. or noradrenaline. Suitable cases for research exist in all mental hospitals, but they need to be selected individually by the psychiatrist, and then everything will depend on first-rate ward supervision, so that questions of food intake and urine collection and detailed clinical change will be answerable. There is no doubt from the work already done that biochemical abnormalities are there to be discovered. The kinds of facts to look for are becoming clearer. Now we need the people willing to look, and some laboratory facilities.

UNIQUE INSTITUTION

There can hardly be a country in the world that has not benefited from the London School of Hygiene and Tropical Medicine. As the latest annual report[1] of this unique institution shows, members of its staff are constantly off on their civilizing missions to improve health in distant countries, former students occupy posts in many remote places, and medical men and women from overseas are welcomed at the courses of instruction. In Great Britain itself the influence of the School is felt in many branches of industry, for much research is being conducted into detecting and removing hazards to health in mine and factory.

An important function of the school is to maintain reference collections of organisms that cause or transmit disease. One of these collections comprises arthropods —insects and the like—and it is appealing for more to be sent from overseas. Former students have been generous in devoting much time and labour to this task, and the good work must continue if the School is to be well equipped for instructing future generations. Research into tropical medicine during the year has included investigations into amoebiasis, sprue, and schistosomiasis, as well as the ever-present, if diminishing, malaria.

The department of public health has continued to run small research projects by means of study groups of its postgraduate students. Some of the conclusions that come out of these are that smoking is commoner among secondary modern than among grammar school children; wives worried because they were given too little information about their husbands' illnesses; and health hazards were "numerous" in some small factories investigated.

[1] *Report for the Year 1957-8*, London School of Hygiene and Tropical Medicine, 1959.

TRANSMISSION OF L.E. FACTOR

At the children's party, when a white rabbit may find itself transmitted from a folded cloak to the interior of a top hat, the thing itself, the amiable rabbit, is used as the evidence for transmission. To the scientist, on the other hand, transmission is often the earliest and often the only evidence of existence; as Pasteur showed, the factor determining transmission reveals the nature of what we are transmitting. The factor in the shed serum of patients with systemic lupus erythematosus which causes their own and other nuclei to become featureless has been under progressively intensive study for the last ten years. Hungarian workers[1] have now been able to transmit this factor to three patients with cancer by transfusing them with between 140 and 200 ml. of serum from a patient with systemic lupus erythematosus. It is of interest that typical L.E. cells could be found in the shed blood within two hours of the transfusion; this phenomenon reached a maximum at 6–24 hours and then slowly disappeared. However, L.E. cells could be found up to 27 days in one patient.

The mere fact of transmission is not surprising, for it is well known that all nuclei are susceptible—autologous, homologous, and heterologous as far down at least as the frog. No one seems yet to have tried the docile amoeba; this perhaps might be rewarding, but it must be remembered that nuclear damage is necessary and also that complement is necessary for phagocytosis. Of special interest is the transmission of the factor through serous membranes and other natural barriers, because this gives some indication of its molecular size. L.E. cells have been detected in pericardial effusions and, by a number of authors, in infants born to mothers with systemic lupus erythematosus. This phenomenon may last up to seven weeks.[3–5] Transplacental transmission seems to be a passive transfer of gamma globulin (which the L.E. factor has been shown to be), and the period is comparable with the half-life of gamma globulin.[6] The somewhat similar antibody-like

[1] Bencze, G., Cserhati, S., Kovacs, J., and Tiboldi, T., *Ann. rheum. Dis.*, 1958, **17**, 426.
[2] Seaman, A. J., and Christerson, J. W., *J. Amer. med. Ass.*, 1952, **149**, 145.
[3] Bridge, R. G., and Foley, F. E., *Amer. J. med. Sci.*, 1954, **227**, 1.
[4] Berlyne, G. M., Short, I. A., and Vickers, C. F. H., *Lancet*, 1957, **2**, 15.
[5] Mijer, F., and Olsen, R. N., *J. Pediat.*, 1958, **52**, 690.
[6] Wiener, A. S., and Gordon, E. B., *J. Lab. clin. Med.*, 1957, **49**, 258.
[7] Den Oudsten, S. A., van Loghem-Langereis, P. E., and Dorfmeijer, H., *Vox Sang. (Basel)*, 1958, **3**, 192.
[8] Glasov, S., and Gechman, E., *New Engl. J. Med.*, 1956, **255**, 936.
[9] Griffin, S. W., Ulloa, A., and Holley, H. L., *Arth. and Rheum.*, 1958, **1**, 544.
[10] German, J. L., *J. exp. Med.*, 1958, **108**, 179.
[11] Gross, L., in *Contributions to the Medical Sciences*, New York, 1932, **2**, 527.

substances in the serum of patients with rheumatoid arthritis—the Rose–Waaler factor—in contrast do not pass the placental barrier. S. A. Den Oudsten and his colleagues[7] cite an especially instructive instance in which a mother with both L.E. cell and Rose–Waaler factors in her serum passed the former to her twins but not the latter, the likely explanation being a difference in molecular size. The L.E.-cell factor is probably an ordinary gamma globulin with a sedimentation constant of 7S, whereas the Rose–Waaler factor is a much larger molecule with a sedimentation constant of 19S, probably in combination with another protein to make a molecule of 22S.

The babies with circulating L.E. factor, as also the Hungarian recipients, seem to suffer no ill effects at least for periods up to several months. Familial lupus erythematosus is uncommon, and recorded cases have been of parent and child only much later in life.[8 9] However, after injection of preformed L.E. cells into the rabbit, J. L. German[10] has produced haematoxylin bodies in the kidneys, and the L.E. cell is believed to be the precursor of the haematoxylin bodies first described as specific for lupus erythematosus by L. Gross in 1932.[11] This procedure might therefore produce functional change in the kidneys. But how the L.E. factor originates is another and more difficult problem.

REHABILITATION OF PARAPLEGICS

The Coal Industry Social Welfare Organization has recently published a report on a survey of paraplegic mineworkers carried out in 1954 and 1955 under the direction of Dr. Alan G. Hardy. The main purpose of the survey was "to obtain an appreciation of the social needs of these men living under home conditions, and where possible to relate these needs to different degrees of their disability." As was to be expected it was found that their needs varied with their disability, their circumstances, and their personality, and that each paraplegic had to be treated as an individual. There were 497 men in the series: in 253 the paraplegia was described as complete and in 244 as partial. Most had some degree of incontinence, 136 had sores, 166 could not walk, and 32 were confined to bed. There was a definite fall in the rate of survival after fifteen years, and most of those over 45 years of age were "partially" affected. The report suggests, but does not stress, the better position of those who had been admitted to a spinal injuries unit. Like most other disabled persons, those who have not had the advantages of modern methods of treatment tend to live their lives at a lower level of health than those who have. To decide that no further medical improvement is possible without obtaining expert advice is unfair to the patient. The routine medical examinations that are desirable are best carried out at a centre where expert knowledge and skill is available, but this is by no means common practice.

To make the paraplegic patient one with his family and with the community as a whole is the aim of rehabilitation. As always, success is more likely if a positive plan can be carried out from the beginning without interruption. Several statutory bodies are concerned with the welfare of paraplegics, and a co-ordinated scheme is essential for the smooth operation of any rehabilitation programme. Delay in the prescribing and supplying of invalid chairs is given in the report of the recent survey as an example of the kind of incoordination which a little foresight could avoid. The more mobile the patient the better, and the supply and maintenance of chairs and powered tricycles could be improved, though the new arrangement for repairs to be carried out at local ambulance depots should be helpful.[1]

A medico-social service of high quality is needed to help with both physical and psychological adjustment and with the problems of the patients' relations. The report rightly pays tribute to the wives of the paraplegic miners. Out of 380 cases requiring nursing, this was carried out by the wife in 203 cases. Extra laundering of one kind and another was needed in 75% of cases. Equipment for home nursing was necessary for the "adequate domestic resettlement" of about 85% of the cases, and nearly half of the patients had no special housing amenities. These figures give some indication of the day-to-day difficulties with which the patient and the family have to contend. The amount of help which local authorities give to the handicapped varies from one area to another, and this lack of uniformity is a cause of relative hardship in some cases.

Out of 325 men considered fit for employment only 74 were working or in training, and, as has been found with other disabled men, there was no striking physical difference between those employed and those unemployed. Lack of suitable work, lack of economic advantage, and the age of the patient were all factors which reduced the total of the employed. The reason for unemployment in 116 cases was ascribed to being "mentally unprepared." It would be interesting to know how many of these men had had the services of an experienced medico-social case worker. For those incapable of working for gain some form of diversional occupation should be available.

Because of the schemes of the Coal Industry Social Welfare Organization the paraplegic mineworker has many benefits not enjoyed by those in other occupations who become paraplegic. In the same way the pensioned paraplegic—from the Forces or industry—is in a much more favourable position financially than the non-pensioner: the survey found that benefits paid to patients injured in non-industrial accidents were inadequate for ordinary daily needs. The paraplegic housewife and the paraplegic child have also to face difficulties which are in some ways greater than those of the industrial worker. Facts brought out in this survey show that the needs of the individual paraplegic patient are not always being fully met, and that better co-ordination of the medical, social, and welfare services could lead to useful improvements. As to the attitude of the community, the report recommends more understanding help and less embarrassing pity.

[1] *Report of the Survey of Paraplegic Mineworkers*, Coal Industry Social Welfare Organization, 5, Hobart Place, London, S.W.1.

Clinicopathological Conference

A COMPLICATED CASE OF CIRRHOSIS

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with cirrhosis of the liver complicated by chronic mental and neurological changes (Case No. 164,948; P.M. No. 8,174). Towards the end of his illness cardiac enlargement developed. These complications are the main subjects discussed.

Clinical History

Dr. SHEILA SHERLOCK: This man was a 39-year-old fitter. His medical history begins in 1945, when, while in the Army in India, he contracted malaria and was found to have an enlarged spleen. In 1947 he was said to be jaundiced and the splenomegaly was still present, though there was no evidence of active malaria. A loud, continuous "venous hum" was heard over the upper abdomen, associated with a palpable thrill, and because of this interesting sign he co-operated in many medical demonstrations to newly enrolled R.A.M.C. officers. He was discharged from the Army and remained well until 1954, when he became increasingly tired, dysarthric, and tremulous. He was irritable and paranoid, with uncontrollable outbursts of violence, usually at night.

In August, 1954, he was admitted to Hammersmith Hospital confused, disorientated, and unable to give a history. He showed a gross "flapping" tremor of the outstretched hands; muscle tone and reflexes were increased and ankle clonus was elicited; plantar responses were flexor. There was excessive salivation and a very strong smell to his breath (fetor hepaticus). Veins in the abdominal wall were not visible. The spleen was enlarged almost to the umbilicus and the liver impalpable. A soft murmur was occasionally heard over the right upper abdomen. He was thought to be suffering from chronic portal-systemic encephalopathy.* This condition occurs in patients with cirrhosis who have developed large portal-systemic venous channels. These allow intestinal products (probably nitrogenous) to bypass the liver and so reach and poison the brain. The diagnosis must be confirmed by demonstrating cirrhosis, a large portal collateral circulation, and intolerance to feeding nitrogenous substances.

INVESTIGATIONS

Liver Disease.—Serum bilirubin (0.8 mg./100 ml.) and albumin (3.7 g./100 ml.) were normal, but aspiration liver-biopsy sections showed irregular fibrotic bands strongly suggesting cirrhosis. There was a slight excess of iron in the liver cells.

Portal Circulation.—Trans-splenic venography† showed a patent portal vein, gastro-oesophageal collaterals, and a most remarkable enlargement of the umbilical vein which arose from the left branch of the portal vein and passed towards the umbilicus (Fig. 1). Blood rushing through this vein was presumably responsible for the venous hum and thrill. Barium-swallow examination failed to reveal oesophageal varices. The pressure in the spleen, which closely reflects portal venous pressure, was normal (12 mm. Hg).

Sensitivity to Nitrogenous Substances.—The patient's neuropsychiatric condition worsened when dietary protein was increased to 100 g. daily and improved when it was reduced to 20 g. daily.

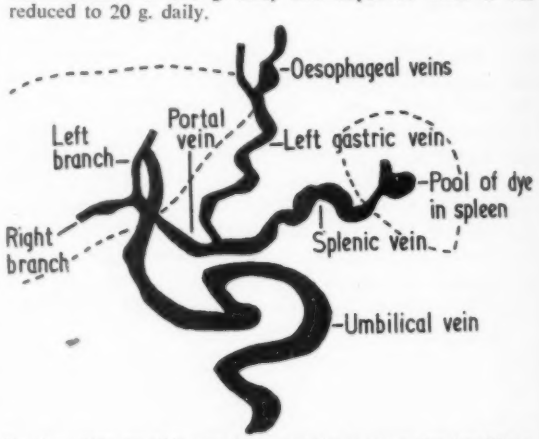

FIG. 1.—Diagram of trans-splenic portal venogram showing filling of oesophageal veins from the left gastric vein, and of the umbilical vein from the left branch of the portal vein.

SUBSEQUENT COURSE

The patient gradually improved when receiving only 60 g. dietary protein daily. He was advised to keep his bowel motions loose. He continued at work until April, 1956, when progressive mental deterioration and inability to use fine tools necessitated readmission to hospital. There was little improvement when dietary protein was reduced, and, when he continued slowly to deteriorate on a protein intake of 50 g., treatment with neomycin sulphate was started. This was given on the assumption that much of the cerebral intoxication was due to products of intestinal bacterial action on nitrogenous substances. Within three days the fetor hepaticus and tremor had disappeared and he had improved mentally. After a week he felt fitter than at any time since 1954. Between June, 1956, and April, 1957, he received neomycin and worked full-time without tremor. In December the dosage of neomycin was decreased with no ill-effect (Fig. 2). On January 12 the neomycin was stopped and replaced by purgatives. (Neomycin causes loose stools and might have been acting only as an expensive purgative.) However, one week after stopping the antibiotic he again deteriorated and treatment with neomycin had to be re-started. He again improved and remained at work until May, 1957, when he was once more admitted to hospital.

There was now definite biochemical evidence of liver failure, with a raised serum bilirubin value (4.9 mg./100 ml.) and a depression of the serum albumin level to 2.6 g./100 ml. He also complained of dyspnoea and substernal pain on exertion, and there was gross oedema of the legs. The heart was not clinically enlarged and a chest radiograph was normal. Blood pressure was 160/50 mm. Hg. Auscultation revealed a loud systolic murmur in all areas, which was of ejection type along the left sternal border (Fig. 3). There was a presystolic gallop rhythm. An electrocardiogram

*Sherlock, S., Summerskill, W. H. J., White, L. P., and Phear, E. A., *Lancet*, 1954, **2**, 453; Summerskill, W. H. J., Davidson, E. A. Sherlock, S., and Steiner, R. E., *Quart. J. Med.*, n.s., 1956, **25**, 245

†Atkinson, M., Barnett, E., Sherlock, S., and Steiner, R. E., *Quart. J. Med.*, n.s., 1955, **24**, 77; Turner, M. D., Sherlock, S., and Steiner, R. E., *Amer. J. Med.*, 1957, **23**, 846.

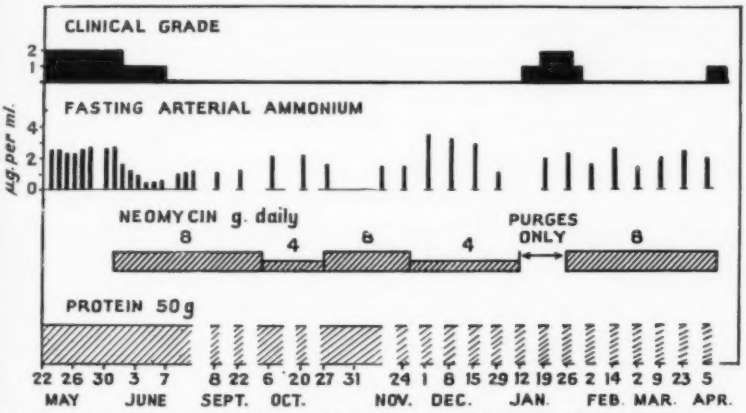

FIG. 2.—Effect of neomycin sulphate on clinical course and fasting arterial-blood-ammonium levels. Dawson *et al.*, 1957 (see footnote to p. 572).

suggested gross left ventricular hypertrophy with possible ischaemic changes. Further investigation showed a very high cardiac output (9.4 l./min.) and a normal saturation of the arterial blood with oxygen, and the peripheral vascular resistance was calculated to be very low. These findings suggested a very hyperdynamic circulation. Improvement again followed rest in bed, neomycin, and restriction of dietary protein, the patient being able to leave hospital but never to resume work.

The final admission was in October, 1957. H. family had contracted influenza and on the day of admission the patient became febrile, with cough and increasing confusion. He was given prophylactic penicillin with the rest of his family. A chest radiograph showed extensive bilateral consolidation consistent with bronchopneumonia. Erythromycin was given in addition to penicillin, but sputum culture showed a staphylococcus resistant to penicillin, chlortetracycline, tetracycline, and erythromycin. There was some diarrhoea but staphylococci were not found in the stools. He died five days after admission.

Clinical Diagnosis

(1) Laennec's cirrhosis of unknown aetiology.
(2) Cruveilhier–Baumgarten syndrome.
(3) Chronic portal-systemic encephalopathy.
(4) Staphylococcal pneumonia complicating influenza.

Post-mortem Findings

Dr. J. G. AZZOPARDI: The body was that of a thin middle-aged man with some blotchy pigmentation over the shins, mild oedema of the legs, and a slightly distended abdomen. The umbilical vein was prominent and the subcutaneous tissues generally were slightly oedematous.

The pericardial sac contained 50 ml. of straw-coloured fluid. The *heart* weighed 597 g. All its chambers had thickened walls, that of the right ventricle measuring 5 mm. at the conus and that of the left ventricle 23 mm. at the base. There was no valvular lesion to account for the hypertrophy. Macroscopically the myocardium was pale brown with occasional small fibrous streaks; microscopically the picture was one of myocardial hypertrophy with scattered foci of fibrous scarring, possibly ischaemic. There was a very small amount of iron in the muscle fibres at the nuclear poles. The *coronary arteries* showed slight to moderate atheroma without luminal narrowing, the *aorta* slight atheroma only.

The right pleural cavity was normal; the left contained 100 ml. of slightly murky brown fluid. The macroscopic appearance of the *lungs* suggested patchy consolidation of the left lower lobe and to a lesser extent of the right lower lobe. Histological examination confirmed the patchy consolidation, with an alveolar exudate consisting of mononuclears, red cells, and fibrin. There was no purulent reaction and no cocci were visible with Gram staining. The appearances were consistent with a viral infection. The alveolar and bronchiolar walls were congested and oedematous.

The peritoneal cavity contained 1,400 ml. of limpid, golden-yellow fluid. There were prominent tortuous *varices* around the adventitia of the lower half of the oesophagus; these were not prominent on the mucosal aspect. An enormously dilated, tortuous umbilical vein ran into the falciform ligament. The haemorrhoidal veins, however, were not distended. Macroscopically the small and large bowels were normal. Histologically the gastric mucosa was normal, with a moderate amount of iron in the peptic and, to a lesser extent, the oxyntic cells; the mucous neck cells were normal. The jejunal mucosa was also normal, with no free iron. There was, however, a conspicuous excess of lipofuscin in the longitudinal muscle coat and in the muscle of the vein

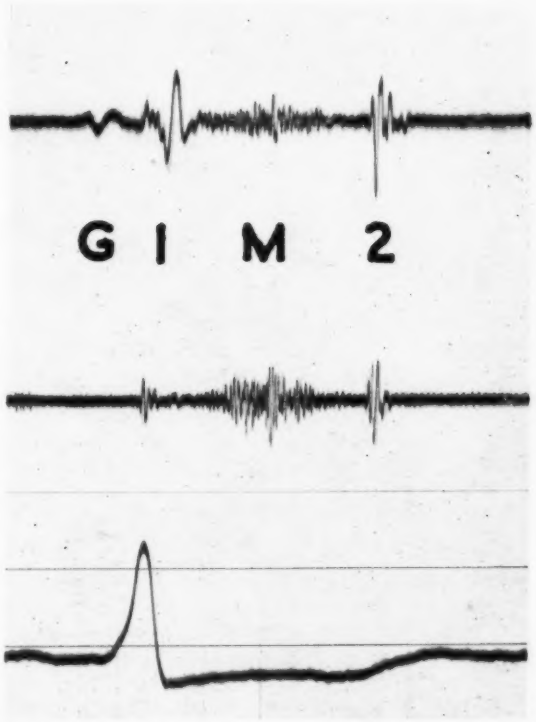

FIG. 3.—Phonocardiogram. From above downwards, low frequency record, high frequency record, electrocardiogram lead II. 1, first heart sound; 2, second heart sound; M, ejection type systolic murmur; and G, presystolic gallop. Murray *et al.*, 1958 (see footnote to p. 571).

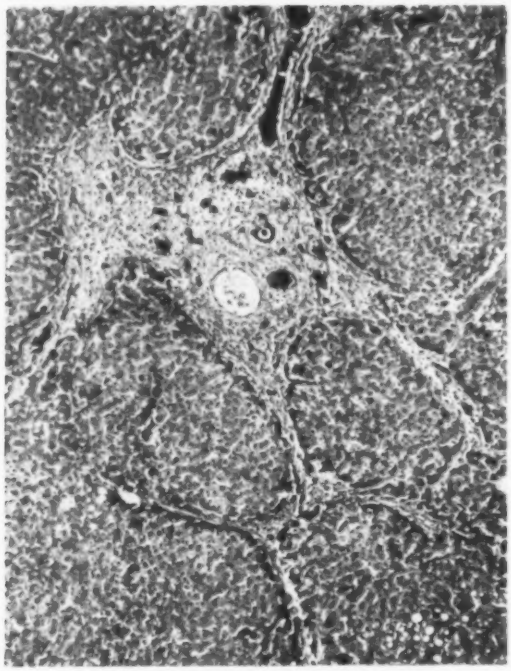

FIG. 4.—Section of liver to show cirrhosis. (×57.)

walls. The *liver* weighed 1,303 g. and had a uniformly fine cirrhotic appearance with nodules averaging a few mm. in diameter; the colour was fawn; and there were no infarcted nodules. The biliary passages were normal. Some plaques of fibrous thickening were present in the endothelial lining of the portal and superior mesenteric veins, with some calcification in one plaque. The hepatic veins were normal. Histologically there was portal cirrhosis of moderate severity (Fig. 4), not very active, with only slight evidence of degeneration and regeneration. There was a moderate amount of iron pigment patchily distributed in the hepatic cells (Fig. 5), but none in the Kupffer cells, fibrous tissue, or bile ducts. The *pancreas* was bright orange-yellow, and showed microscopically a mild interlobular and intralobular interstitial fibrosis. There was a moderate amount of iron in the acinar cells and, to a lesser extent, in the islet cells. There was an excess of lipofuscin in a few vein walls.

The *kidneys* were enlarged, each weighing 222 g. Apart from a wide cortex (8 mm.) they were macroscopically normal. This was confirmed histologically. There was a minimal amount of iron in the glomerular filtrate and in an occasional proximal convoluted tubule, where it varied from a diffuse, pale blue haze to fine granules. The *testes* were macroscopically normal: they showed slightly diminished spermatogenesis, but there was no iron in the vessels or elsewhere.

The *spleen* was enlarged to 741 g. Its capsule showed slight patchy thickening, the pulp was pinkish-brown and firm with conspicuous lymphoid follicles, and siderotic nodules were few. Histological examination showed an excess of iron in macrophages in the capsule, an occasional siderotic nodule due to local haemorrhage, minimal iron in the reticulo-endothelial cells generally, and a slight increase in the reticulin framework. The only *lymphadenopathy* was in the portal and coeliac nodes, which measured up to 10 mm. in length. In the portal nodes there was a moderate amount of iron outlining the sinuses. The mediastinal nodes showed sinus hyperplasia but no free iron. The sternal *marrow* was normal, with no free iron.

The *adrenals* weighed 6 g. each, and, apart from depletion of cortical lipoid, were normal. There was an insignificant amount of iron in the zona glomerulosa. The meninges, *brain* (1,102 g.), and circle of Willis were normal.

Pathologist's Diagnosis

(1) Portal cirrhosis. Gross portal-systemic anastomoses (enormous umbilical vein, paraoesophageal varices). Splenomegaly. Ascites.

(2) Influenzal bronchopneumonia.

(3) Cardiomegaly due in part to high output failure.

(4) Pancreatic fibrosis.

(5) Siderosis (moderate) of liver, pancreas, coeliac lymph nodes, and stomach. Lipofuscin excess in smooth muscle of jejunum.

Discussion

Dr. SHERLOCK: This patient suffered from some form of cirrhosis with an extensive portal-collateral circulation. Investigations clearly established that the neuropsychiatric changes were those of chronic portal systemic encephalopathy. His condition improved greatly after the introduction of dietary protein restriction and of neomycin,* but this treatment failed to halt the progressive liver-cell failure. Death in liver failure is the usual fate of patients with this syndrome.

The term Cruveilhier–Baumgarten syndrome is applied to the association of a patent umbilical vein with a venous

*Dawson, A. M., McLaren, J., and Sherlock, S., *Lancet*, 1957, 2, 1263.

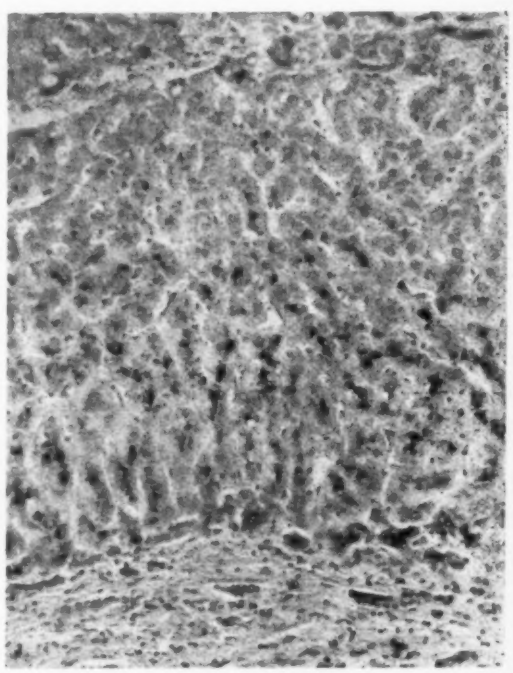

FIG. 5.—A higher magnification to show haemosiderin granules in hepatic cells of the peripheral zone. (×150.)

hum heard over the abdominal wall and producing a thrill. Dilated veins in the abdominal wall are usually also seen. This patient had the main features of the syndrome but without the dilated veins in the abdominal wall. The usual cause is obstruction to portal blood-flow due to cirrhosis of the liver. The dilated umbilical vein in this case had reduced the portal venous pressure, and the intrasplenic pressure was therefore normal. The oesophageal collaterals seen in the splenic venogram were perioesophageal rather than submucosal, which was why the barium-swallow examination was negative. He ran no risk of bleeding from oesophageal varices.

We must now consider whether this man had "classical haemochromatosis." Clinically, this had not crossed our minds, so when in retrospect this question arose I reviewed the original liver-biopsy sections. Sure enough there were increased amounts of iron in the liver cells, but I do not regard them as sufficient for a diagnosis of classical haemochromatosis; in particular, I did not see the great clumps of iron in the fibrous tissue bands, usually noted in haemochromatosis. Clinically this man was not pigmented; he did not have testicular atrophy and his youngest child was aged 4; and there was no glycosuria. The liver in haemochromatosis is characteristically large and not small, and the development of a large portal collateral circulation is unusual The cardiac features of haemochromatosis are ischaemic, with irregularities of rhythm, congestive failure, and a low cardiac output. I do not think this patient suffered from classical haemochromatosis, but I am at a loss to explain the large quantities of iron in the tissues: a cirrhotic liver does occasionally contain an excess of iron, but the amount found in this patient is unusual. In 1945, Veryan Walshe and I noted that, among the undernourished in Germany, iron in the liver cells was almost the sole hepatic abnormality. Perhaps this patient's three years' protein deprivation had increased the iron deposition in his liver.

I find it difficult to accept the terminal illness as a virus pneumonia. I should be interested to hear comments on the patchy consolidation seen in the chest radiograph, and the presence of a resistant *Staphylococcus aureus* in the sputum must also be explained.

Professor J. McMICHAEL: It is frightfully difficult, isn't it, to settle the cause of pneumonia at necropsy, whether it was bacterial alone or a mixture of virus and bacteria?

Professor C. V. HARRISON: I would be prepared to say that this was definitely not staphylococcal, in the absence—the total absence—of polymorphonuclears.

Dr. SHERLOCK: This patient always had a leucopenia perhaps due to "secondary hypersplenism"; even terminally the total leucocyte count was only 2,000/c.mm. He may have had difficulty in producing a polymorph response to bacterial infection.

Dr. C. PALLIS: How often does a portal shunt of this magnitude develop in the presence of clinically mild cirrhosis, and without a portal vein thrombosis?

Dr. SHERLOCK: Well, this is a very rare condition and I cannot give the frequency. I suppose I have seen five examples of dilated umbilical veins causing abdominal murmurs. They were all demonstrated by trans-splenic portal venography. In every instance cirrhosis was present, but it was usually well-compensated.

Professor McMICHAEL: You mean that the Cruveilhier–Baumgarten syndrome is really just a peculiar anatomical pattern of venous collaterals in otherwise fairly ordinary cirrhosis of the liver?

Dr. SHERLOCK: Yes.

Professor HARRISON: Is it possible that the undue iron absorption in this man was due not merely to the depletion or inadequacy of his protein intake but to the treatment with neomycin?

Dr. SHERLOCK: Neomycin therapy causes diarrhoea and steatorrhoea, so I would expect iron absorption to be decreased rather than increased.

Professor McMICHAEL: This case is very complex. It is difficult to account for a 600-g. heart on the high-output state that often develops in cirrhosis of the liver. The high cardiac output is rather a terminal picture, and I wouldn't have thought that it could have been responsible for this great enlargement of the right and left heart. He also had very extensive myocardial fibrosis, which may be part and parcel of haemochromatosis.

Dr. AZZOPARDI: At the post-mortem examination I seriously considered the possibility of an early haemochromatosis, largely because of the macroscopic staining reactions which were so very striking. The sensitivity of the iron stain, combined with the natural pale colour of the pancreas, gave an exaggerated impression of the amount of iron there. I find it difficult now to see how such a definite cirrhosis with such marked signs could be found in the presence of so relatively little iron if the defect in iron metabolism was primary. I don't know what would happen, of course, if a person who was going to develop haemochromatosis happened to have piles from which he bled profusely. Would he develop haemochromatosis at all? In other words, is the cirrhosis in haemochromatosis directly related to the iron excess or is it due to an associated defect independent of the amount of iron? If the former view is correct, this man is unlikely to have had haemochromatosis.

Dr. SHERLOCK: He wasn't bleeding from the gastro-intestinal tract.

Dr. AZZOPARDI: No, but I'm just postulating it. Supposing, instead of absorbing daily the 6 mg. (or whatever the amount may be) that a patient with haemochromatosis absorbs instead of the normal 1 mg., such a patient had a positive balance of only 2 or 3 mg. owing to loss of iron through bleeding, would he still develop haemochromatosis at the same stage of his life without massive iron deposits? The evidence suggests that he would not.

Dr. SHERLOCK: There are many references to cardiac changes in haemochromatosis, but the heart size is usually small and the cardiac output low. I think this man's circulatory changes fit in with results reported from this school.* Seventeen patients with cirrhosis (including this patient) were described. In half the patients cardiac output was increased and there was evidence of increased peripheral blood and of ejection systolic murmurs. Incidentally, this man's cardiac output fell and his peripheral vascular resistance increased as his liver function improved in hospital.

Dr. P. S. KINCAID-SMITH: I saw the 17 cases mentioned by Dr. Sherlock, which were written up by Dr. J. F. Murray and his colleagues last year, and I think that Dr. Murray would agree that this patient was somewhat atypical. He was the only one with a loud, unequivocal atrial sound, and in addition he had clinical

*Murray, J. F., Dawson, A. M., and Sherlock, S., *Amer. J. Med.*, 1958, **24**, 358.

and electrocardiographic evidence of cardiac hypertrophy. He seemed to be a rather extreme example of the high cardiac output syndrome they described. I also looked through about 20 cases of chronic liver failure three years ago and found that the heart weights were not significantly increased. It seems, therefore, that one must consider some cause other than liver failure and high output state to explain the considerable cardiac hypertrophy in this case.

Professor E. J. KING: Could the very low protein intake cause a partial failure of haemoglobin formation? He may have been destroying haemoglobin during the long period of protein restriction faster than he was making it. He was anaemic towards the end.

Dr. SHERLOCK: May I comment on Professor King's question? I may be wrong about this, but I understood that in severe starvation haemoglobin is formed far preferentially to other protein. In extreme wasting one does not in fact meet anaemia, and I thought that came out in Professor R. A. McCance's study in Germany after the war. The second point is that haemolysis does of course occur sometimes in cirrhosis. In this particular patient we have no positive proof of this. I don't think he was investigated from that point of view, but there was not much iron in the spleen, which would, I think, be against haemolysis. On the other hand, the leucopenia does suggest that he was in fact suffering from what is loosely called secondary hypersplenism.

Professor MCMICHAEL: That is not uncommon in your cirrhotics, I believe, Dr. Sherlock?

Dr. SHERLOCK: Platelets were 60,000/c.mm., reticulocytes were 1–2%. I should have thought that the iron in the pancreas and liver was not in favour of increased absorption in this particular case.

Professor KING: Is there any evidence, Dr. Sherlock, if one increases the blood ammonia, whether that increase is reflected uniformly throughout the body, or are there greater increases in some tissues than in others? Could such an increase possibly account for a deposition of iron in one tissue rather than another?

Dr. SHERLOCK: Peripheral tissues take up ammonium and there is therefore an arteriovenous difference. Because of variable tissue uptake, the arterial rather than the venous level is usually measured in liver disease.*

A PHYSICIAN: Might the pigment be malarial pigment?

Dr. AZZOPARDI: Malarial pigment looks different. It is thought to be related to haematin, and certainly doesn't give a positive iron reaction with Perles's stain. Apart from that, it is deposited mainly in the reticuloendothelial system. The iron is just in the wrong place in this case. In haemochromatosis it is present predominantly in the liver and pancreas. If you give iron experimentally—for instance, intravenously—most of it at any rate is usually stored in the spleen, Kupffer cells, bone marrow, and so on. The bone marrow in this case was completely negative for iron.

A PHYSICIAN: Perhaps he was treated with iron by mouth, and would not the iron then accumulate in the liver and pancreas perhaps?

Dr. SHERLOCK: He hadn't had any iron medication for the last five or six years anyway.

*Dawson, A. M., De Groote, J., Rosenthal, W. A., and Sherlock, Sheila, *Clin. Sci.*, 1957, **16**, 418.

Professor MCMICHAEL: Is there any pathological finding in the intestinal wall in haemochromatosis to suggest increased absorption of iron or failure to reject it?

Dr. AZZOPARDI: You get an excess of iron in the stomach, of course, but very little or none in the jejunum as opposed to what one finds in some other types of cirrhosis—the nutritional cirrhosis of the Bantu, for instance.

Professor MCMICHAEL: We are in a dilemma in this case. The whole clinical course was not in the least like haemochromatosis, yet there were certain odd features such as the cardiac manifestations which are unusual for an ordinary cirrhosis. At necropsy he had a heavy deposition of iron justifying a diagnosis of haemochromatosis, but this is in conflict with the whole clinical course. Are we going to say that this man had primary cirrhosis of the liver, developing in some peculiar way haemochromatotic manifestations; or are we to say that the deposition of iron was one of the metabolic difficulties that resulted from his cirrhosis, as a very unusual manifestation? This is very difficult to sustain, because I don't think we have seen this sort of thing before. We ought to put some sort of final interpretation on what we have seen. What do you think, Dr. Sherlock?

Dr. SHERLOCK: The amount of iron present in this patient's liver at the time of the original biopsy in 1954 was not commented upon in the report given by Professor J. H. Dible. If he had thought that it was a bit unusual he would have remarked on it. I would like to see iron stains on the livers of the last 50 patients with cirrhosis who have died in this hospital.

Dr. AZZOPARDI: I have stained the liver, pancreas, and spleen of 20 cirrhotics for iron. These were largely males of comparable age in whom there had been no bleeding, except in some cases during the 18 hours preceding death. About a third contained a significant amount of iron in the liver, mostly in the Kupffer cells, and some of them contained iron in the spleen. There was one peculiar case with rather a large amount of iron in the hepatic and pancreatic parenchyma, but he did not have pancreatic fibrosis. So I am afraid that the results on this small series are inconclusive. I think one should really do iron stains on all cirrhotic liver biopsies; any suggestion of an excess of iron could then be investigated.

Professor HARRISON: Can I make just one further point? Are you saying that there was less iron in the liver when the biopsy was done than there is now?

Dr. SHERLOCK: It looks about the same.

A STUDENT: Can I make a suggestion? When this man was going round the various Army units, do you think he was treated with iron? He might easily have been, for his malaria and his enlarged spleen in a loose sort of way. Once you take iron into the body it doesn't come out, so the whole picture might possibly be due to an increased intake of a previous decade.

Dr. M. D. MILNE: It makes one worry that there is even a certain amount of pathologists' observer-error in the diagnosis of haemochromatosis. Perhaps the dilemma could only be resolved by the very laborious method of estimating the actual iron content of various organs. I agree this would involve a tremendous amount of work, but it would obviously put the diagnosis on a quantitative basis.

Dr. AZZOPARDI: I don't think that even that would solve the problem entirely, for the quantity of iron *per se* does not matter all that much. The recent Glasgow work,* for instance, shows that patients receiving multiple transfusions over a period of years can have iron deposits as massive as those seen in haemochromatosis without developing cirrhosis.

Dr. MILNE: So what we are saying in the end, then, is that it is a matter of opinion?

Dr. AZZOPARDI: Unless one investigates the case during life. That, I think, is the value of carrying out iron stains on all cirrhotic livers diagnosed on biopsy.

Professor HARRISON: I see no problem here. Has this man a haemochromatosis or not? There is not nearly enough iron to cause cirrhosis, if that is how you interpret haemochromatosis. I think he has got a lot too much for the average case of cirrhosis, but I don't think there is any question of calling him a case of haemochromatosis with resultant cirrhosis of the liver. He has had some other primary cirrhosis and developed haemochromatotic features.

Professor MCMICHAEL: Shall we call him, then, a case of hepatic cirrhosis with siderosis?

We are grateful to Drs. J. P. Shillingford and B. E. Heard for assistance in preparing this report, and to Mr. W. H. Brackenbury for the photomicrographs.

*Cappell, D. F., Hutchison, H. E., and Jowett, M., *J. Path. Bact.*, 1957, **74**, 245

MILROY LECTURES

ROYAL COLLEGE OF PHYSICIANS

The Milroy Lectures in State Medicine and Public Health were given this year, on February 3 and 5, by the Director-General of Public Health for South Australia, Dr. A. R. SOUTHWOOD. He has held this position since 1931, and it is therefore significant that out of this rich epidemiological experience the subject he chose for his lectures to the Royal College of Physicians of London was "The Prevention of Heart Disease."

Heart Disease in Australia

The plan now in public health, said Dr. Southwood, was first to find out what illnesses are common and damaging to the people's health, then to study their direct and contributing causes, and so evolve and institute preventive measures.

Statistics for Australia showed that the certified cause of more than half the deaths there was diseases of the heart and blood vessels. There had been a rapid and continuing decline in deaths from infectious illnesses, including tuberculosis. But deaths from accident and violence had been rising, and these now accounted in Australia for over 70% of all deaths in men aged 15 to 24 years. The trends in England and Wales, the North American countries, and New Zealand were similar. In addition, more people were living into old age: whereas in 1911 only 6.4% of Australians were over 60 years of age, in 1954 the percentage was 12.5.

The main causes of death in the elderly were diseases of the heart, cancer, and accidents: in our ageing populations all those were likely to show an increase.

Heart disease was not a single disease, but a group of conditions. There were the congenital forms, which were becoming better understood and sometimes amenable to treatment. The major groups of heart trouble, however, were those due to rheumatic infection, high blood pressure, and arteriosclerosis. The rheumatic form was becoming less common; the other two groups were increasing.

High blood pressure remained a scourge, and, although there were encouraging signs from the use of some new forms of treatment, its cause and satisfactory preventive measures were yet to be found. Atherosclerotic heart disease was steadily becoming more frequent. It was the basic cause of most of the deaths from heart disease in most countries to-day.

Coronary Atherosclerosis

The results of statistical inquiry were illuminating. Post-mortem examinations indicated that most people past middle life had some degenerative changes in their blood vessels, and the increase in heart disease in death certification was associated especially with blame being put more often on the coronary arteries. Even so, the figures did not signify as grave a situation as might at first appear. The higher proportion of old people, alterations in classification, and the greater medical interest in coronary artery disease—all had conduced to the statistical increase recorded. But, even if coronary atherosclerosis was not more frequent, some increase in coronary thrombosis and consequent acute heart failure did seem to have occurred. Why that was so was the number one problem in heart disease to-day.

Research studies by biochemists had shown the importance of a disordered state involving the fatty constituents of blood and other tissues, arising partly at least from dietary factors. The taking of a large amount of fatty food, especially animal fats, steadily over many years was suspected to be hazardous—but clear proof was still lacking. The kind of fat was important, for the vegetable fats, and especially the unsaturated fats, were probably harmless. Overfeeding of any kind was unwise. Australian aborigines, New Guinea natives, and several other groups had been found to suffer less than "civilized man" from atherosclerosis, and the difference was thought to be in dietary habits rather than racial features.

Ageing was also important; yet fatal heart attacks in young or middle-aged men were common enough to cause concern. People working in active jobs seemed less likely to become victims than those engaged in sedentary occupations. The effects of coronary disease fell twice as heavily on men from 40 to 60 years of age as on women of similar ages, but old women and old men were equally prone.

What could be done to prevent this form of heart disease? So far, medical science could offer no clear or simple plan, and epidemiological and laboratory research must continue, said Dr. Southwood. The observance of what were generally understood as rules for good health—regular habits, steady work, outdoor exercise, temperance in eating and drinking—was the best advice that could be given. If symptoms of disease developed, special medical advice might do something to ward off disaster. "Live sensibly, and avoid all excesses" was the best advice: yet its rigorous observance was no sure safeguard. Many people would prefer to ignore it, and take a chance—and often they appeared to get away with it.

About 80 general practitioners attended a symposium on general practice held at Cambridge earlier this month as part of one of the postgraduate courses run by the university medical school. Of the medical speakers, Lord TAYLOR described the group practice arrangements at Harlow and examined the criteria for "good general practice"; Professor A. LESLIE BANKS surveyed the ancillary services; and Dr. G. E. GODBER spoke about current trends in general practice. Mr. WALTER HAGENBUCH, speaking as an economist, suggested that the absence of a price mechanism in the N.H.S. placed undue responsibility on both patient and doctor; and Dr. L. GLANVILLE WILLIAMS, university reader in English law, discussed the medico-legal aspects of birth and death, euthanasia, and problems arising from the practice of artificial insemination.

Drug Treatment of Disease

MIGRAINE: PART I*

BY

RAYMOND GREENE, M.A., D.M., F.R.C.P.

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The multiplicity of drugs used in the treatment of migraine is a measure of the ineffectiveness of each when used without discrimination. There is no symptom in which it is more necessary for the treatment to be tailor-made. Though the actual mechanism of an attack is understood (vasoconstriction during the premonitory symptoms and vasodilatation accompanying the pain), the switch which initiates the mechanism is far less clear. Indeed, it would appear that there are several possible switches. Allergy, cerebral oedema, autonomic imbalance, endocrine imbalance, physical or mental strain, or shock, fatigue, sudden sensory stimulation (for instance, by bright light), and water retention have all been incriminated. A family tendency is often manifest. A particular personality pattern is often, but not always, present; many sufferers are tense, overconscientious, meticulous, even obsessional, and, by reason of this, easily frustrated, resentful, and dissatisfied. Though it is extremely unlikely that migraine has ever a purely psychological origin, psychological factors are often prominent in the story, and it is certainly true that confidence in the physician and sincere co-operation in the patient are as important in treatment as drugs or hormones. Often the patient must be willing to make great adjustments in his way of life and even to alter sincerely held beliefs and ingrained habits. The patient demanding only a "wonder drug" will fail to obtain more than temporary relief.

It follows that, before the choice of drug is made, the personality of the patient must first be examined and his habit of life reviewed. The circumstances which tend to cause attacks must be studied. They are not necessarily common to any two patients, for situations which are stressful to one may be calming to the other. Sailing a small boat in a rough sea or climbing a difficult rock peak may bring to the one peace of mind and a cessation of attacks, to the other terror and precipitation of pain. Such studies are possible only to the family doctor, for they require months or years to complete and are beyond the scope of the consultant. The latter may at times be useful in confirming the diagnosis and eliminating other causes of cranial pain: the treatment must remain with the constant medical attendant. Apart from the advice which he can give on work and play, on the avoidance of harmful stress and on submitting gracefully to the inevitable, on the diet when this appears to be unsuitable, an embarrassing richness of drugs lies at his disposal.

DRUGS TO REDUCE FREQUENCY AND SEVERITY OF ATTACKS

1. Ergotamine and Its Preparations

Ergotamine tartrate ("femergin," "gynergen"). $(C_{33}H_{35}O_5N_5)_2,C_4H_6O_6$, is an alkaloid obtained from a fungus, ergot of rye (*Claviceps purpurea*), the pharmacology of which is too well known to need description here. It is effective in migraine by reason of its vasoconstrictor effect. It is probable that its effect is potentiated by the addition of caffeine, as in "cafergot," in which 1 mg. of ergotamine tartrate is mixed with 100 mg. of caffeine. In "migril" 2 mg. of ergotamine tartrate is mixed with 100 mg. of caffeine and 50 mg. of cyclizine hydrochloride, an anti-emetic.

Ergotamine tartrate, whether for prophylaxis or for the treatment of acute attacks, should be avoided: (1) In the presence of peripheral vascular disease, hypertension, and coronary disease. It should be used with great caution in all elderly patients. (2) In pregnancy, when, however, dihydroergotamine, which has only a very slight oxytocic effect, may be given instead, at any rate until the seventh month. (3) In thyrotoxicosis, in which it is unwise to add to the circulatory strain already present. (4) In gross sepsis, hepatic and renal disease, and anaemia.

Ergotamine tartrate may be given by injection, by mouth, or by suppository. None of these can safely be given for prolonged prophylaxis, but they may be useful in aborting the expected attack. Patients frequently know in what circumstances an attack is likely to develop—the interview, the board meeting, the first night in the theatre, the first class at the beginning of term. An injection of 0.25 to 0.5 mg. given the night before is often effective. Some patients prefer dihydroergotamine methanesulphonate 0.75–1 mg. Suppositories are often equally effective (e.g., cafergot suppositories). Tablets are the least effective form of therapy, but are occasionally satisfactory in the occasional patient, either alone or combined with caffeine. The maximum initial dose is three tablets, and not more than 10 should be given in the 24 hours preceding the expected stress.

Toxic Effects.—Prolonged prophylactic treatment with ergotamine is fraught with danger. It is capable of producing such prolonged vasoconstriction that thrombosis and gangrene occur. Graham (1956), in his excellent book *The Treatment of Migraine*, gives an impressive list of toxic effects which have been reported: muscle cramps, joint pains, paraesthesiae, cold extremities, intermittent claudication, raised blood pressure, pulselessness, pallor, cyanosis, thrombophlebitis, peripheral arterial thrombosis, gangrene, precordial pain, abdominal pain, coronary infarction, and cerebral thrombosis. None of these sequels is likely to follow the occasional prophylactic use of ergotamine.

The acute toxic effects are likely to be more difficult to control. In some patients, they are less likely to occur when dihydroergotamine methanesulphonate is used, even though twice the dosage may be needed. Whichever preparation is given, a dose high enough to stop the headache commonly causes nausea and vomiting. These side-effects may sometimes be prevented by giving dimenhydrinate ("dramamine")

*Part II, with list of references, will be published next week.

or chlorpromazine ("largactil"). Prednisolone (5 to 25 mg.) given before the ergotamine may be highly effective, relieving not only the nausea but the prostration of the attack if it is not altogether prevented.

2. Diuretics

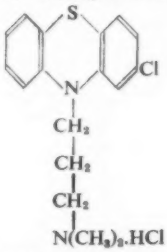
The administration of these drugs is undoubtedly a most useful prophylactic measure in patients whose attacks seem to be related to water retention. Urea is the most useful diuretic, because it retains its efficacy and may be administered for life if necessary. It is best given in doses of 10–20 g. three times a day after food, dissolved in a little hot water flavoured with lime juice.

Urea (or carbamide, $CO(NH_2)_2$) is a natural product of the metabolism of protein and is completely without toxic effect. It often reduces the incidence of attacks of migraine and in occasional cases altogether prevents them. It is a much-neglected remedy.

3. Carbachol

Carbachol, *B.P.* syn. carbamylcholine chloride, $[H_2N.CO.OCH_2.CH_2.N+(CH_3)_3]Cl-$ ("moryl"), is a cholinergic drug, and the rationale of giving it between the attacks is obscure. Yet its value is attested by several authors and by my own experience. It is given in a dosage of 2 mg. three times a day, and in some patients undoubtedly increases the intervals between attacks. It is contraindicated in the presence of cardiac failure and peptic ulcer.

4. Chlorpromazine



The main use of chlorpromazine (largactil) is to offset the toxic effects of ergotamine tartrate. 25 mg. should be given by mouth or by injection a quarter to half an hour beforehand. It can also be given as a suppository of 50 mg. Its use in acute attacks will be described later. "Stemetil" is a chemically related proprietary remedy which has not yet had an extended trial. As a prophylactic 10 mg. is given morning and evening.

(To be concluded)

What vaccinations do you need to travel abroad? The answer is to be found in the new publication of the World Health Organization (W.H.O.), *Vaccination Certificate Requirements for International Travel*, which lists the vaccinations imposed or recommended by some 180 countries and territories from Aden to Zanzibar. Land, sea, and air travel around the world comes under the International Sanitary Regulations promulgated by W.H.O. in 1952. Their aim is to ensure maximum security against the international spread of disease with minimum interference with world traffic. Under these regulations, certificates of vaccination against only three diseases—cholera, smallpox, and yellow fever—may be required. The necessity for one or more of these vaccinations varies according to the country from which the traveller comes and the itinerary he intends to take. The now famous yellow booklet of vaccinations, "The WHO International Certificate of Inoculation and Vaccination," has become as important for the traveller as his passport.

A FOETAL TISSUE BANK

PROBLEMS AND PROSPECTS

BY

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Two of the most fruitful branches of recent research have been concerned with tissue-transplantation immunity and with the effects of radiation on the body. Where these have overlapped there has developed the study of bone-marrow replacement, which, in this new age of radiation, is of obvious practical importance. It is hoped that by transplantation of fresh marrow cells after massive accidental irradiation lives may be saved and, in a similar way, that the scope of high-dosage radiotherapy could be extended.

At an early stage it became apparent that, for donor material, foetal cells might hold definite, even decisive, advantages over adult cells but that other factors might counterbalance these (see Table). Clearly more information was required.

Immunological Considerations

It can be stated as a principle that grafts of living cells exchanged between unrelated members of a species are destroyed after a short interval by an immune response of the host's lymphoreticular system—the homograft reaction. The main exceptions to this rule occur where either the graft is "insulated," as in the cornea, or where the host's immune system is ineffective

Advantages and Disadvantages of Foetal and Adult Haemopoietic Cells for Transplantation

	Adult	Foetal
Quantity	Unlimited. (1) Donor (2) Cadaver	Limited
Quality:		
Activity	Normal adult proportions	Erythro > thrombo > leucopoietic
Stem cells	Low proportion	High proportion
Lymphoid cells ..	Small numbers in marrow	Precursors accompany haemopoietic cells in spleen and ? liver
Tolerance:		
Of graft by host ..	Normal homograft reaction unless modified by radiation, etc.	Homograft reaction possibly slightly delayed
Of host by graft ..	Seldom achieved. Usually "secondary disease"	Better than adult but sometimes "secondary disease"
Genotype availability	Wide range available either (1) fresh from donors or (2) stored from cadavers	Limited to stored tissue

owing to immaturity (in the foetus), disease (agammaglobulinaemia), or damage (irradiation, nitrogen mustards, etc.).

The dose of whole-body radiation needed to suppress the immune mechanism is very high, exceeding the dose which, without marrow replacement, would be fatal. With doses in this range, therefore, marrow replacement becomes simultaneously both possible and essential to survival. This is the basis of bone-marrow replacement therapy. After marrow-assisted recovery a rather complicated situation may develop. The following

events may occur: (1) The irradiated host tissues may slowly recover to form his own blood cells and at the same time the recovering lymphoreticular system may react against the grafted cells. Thus there is a slow return to the original ungrafted state, or, if this reaction is incomplete, there may be a mixture of circulating blood cells. (2) The grafted cells may remain and proliferate normally without reacting against the surviving cells of their new host, who thus becomes a stable chimera. (3) The grafted cells may react immunely against host cells which are foreign to them. This produces the condition of "secondary disease," characterized by wasting and diarrhoea, which is usually but not always fatal.

The factors determining the exact course of events are still somewhat obscure, but it would seem that the dose of radiation, the degree of "compatibility" (both ways) of host and graft, and the number of grafted lymphoid (immunologically competent) cells are, in combination, the determinants.

The virtue of foetal cells lies in their immunological immaturity, so that they are less capable of reacting against their host and causing the aftermath of secondary disease. They also have a second advantage, which remains theoretical and as yet unproved. After high doses of radiation, especially in the treatment of leukaemia, the fatal complication, despite all the measures that can be taken, is usually infection (Thomas, Lochte, and Ferrebee, 1959). This may be attributed in the main to lack of an effectual defensive system, and it is to be hoped that, in these circumstances, foetal lymphoid precursors, tolerant of their new hosts, may yet mature sufficiently to provide some antibacterial defences.

Collection of Human Foetuses

Unfortunately the supply of human foetal tissue is severely limited by stubborn practical considerations. Thus in the first three months of pregnancy the embryo is very small and is seldom to be had in an intact and sterile form. In the last three months, on the other hand, the infant, if not actually so, is held to be potentially viable, and parents' consent to a necropsy is necessary. Discretion in these circumstances calls for some delay, and thus it is seldom possible to obtain fresh tissues from late foetuses. Moreover, it is not yet known whether such foetuses retain their original virtue of adoptive tolerance.

There remains the middle period of pregnancy, from 12 to 28 weeks. A few pregnancies are terminated by hysterotomy at this time, mostly for renal, cardiac, or mental disease; spontaneous abortion is also uncommon. When it does occur a proportion of the foetuses are macerated, but in those that are not the tissues appear to be healthy. Occasional evidence of trauma is seen, and sometimes a foetus, though but recently dead, is found to be infected. With this exception, however, they can be taken as suitable donor material for tissue transplants.

The actual cause of these abortions is in most cases not discovered, and it is likely that a large number, perhaps the majority, are induced. In other cases gynaecological abnormalities may be present, and in some patients mid-pregnancy is the time that habitual abortion occurs. The possible role of blood-group incompatibility, especially in the ABO system, is discussed later.

Whatever the cause may be, foetal death does not precede delivery by very long. We have used, as a rapid test of cell viability, Schrek's (1936) eosin-staining technique. Unstained cells in such preparations are considered viable, and with a suspension of hepatic cells the results are clear-cut. In comparing suspensions from hysterotomy specimens with those from "natural" abortions we have found no significant difference except when there has been delay in obtaining or dissecting the foetus. At room temperature six hours after delivery some decrease in viability is noticed, and at 12 hours most cells are dead. If kept at 4° C. cell death is very appreciably delayed.

It was soon evident that to obtain enough foetuses in a fresh condition an organization would be needed which must cover most of the Greater London area and be alert for 24 hours a day. That this has been achieved is due very largely to the help of the gynaecologists and nursing staff of the many hospitals concerned. On them has fallen the burden of remembering to inform us on the rare occasions when a suitable foetus is available.

Foetal Haemopoiesis

Blood cells in foetal life are derived from many sites of formation. From the accompanying diagram (Fig. 1) and Figs. 2–5 it will be seen that in the specimens available to us the liver is the main organ concerned. It should perhaps be emphasized also that, although there is some decline in the relative proportion of hepatic haemopoiesis after the 20th week, there is little absolute change until at least the 28th week. The spleen by

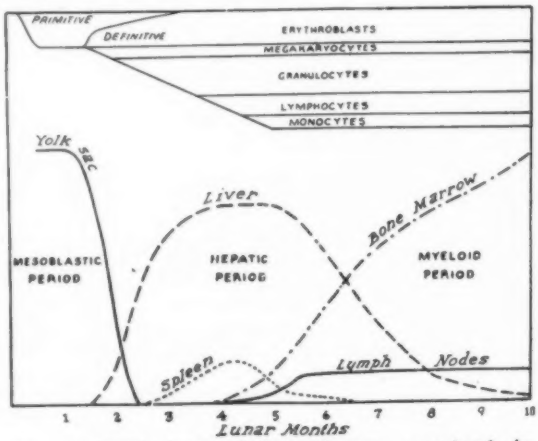

FIG. 1.—Foetal haemopoiesis. Diagram, reproduced by permission, from M. M. Wintrobe's *Clinical Hematology* (Fig. 1), 4th ed., 1956. Henry Kimpton, London.

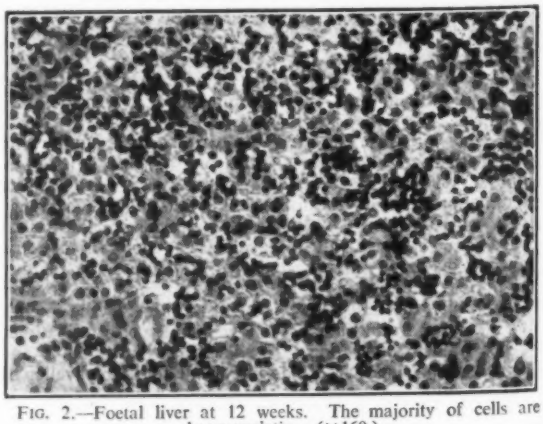

FIG. 2.—Foetal liver at 12 weeks. The majority of cells are haemopoietic. (×160.)

contrast is both small and contains few haemopoietic cells, but by virtue of its lymphopoietic and some myelopoietic activity it may be of supplementary value. Bone marrow itself we have not attempted to use. The total volume of such tissue is never large and is divided up among many bones from which extraction is difficult.

The foetal necropsy is performed with full sterile precautions, and, unless it has been delivered intact in its membranes, the whole skin surface is swabbed with tincture of iodine. The dissection presents no special technical difficulties, but to maintain an adequate exposure a pair of Cawthorne's mastoid retractors has been found useful.

The liver and spleen can be reduced to a cell suspension by pressing gently through a wire mesh of grid size 150 μ. This removes all the stroma and breaks the tissue up into individual cells together with a few small clumps (Figs. 6 and 7). Such clumps can be eliminated by further meshing, but this practice has been discarded, as it damages the free cells. There is no evidence that the clumps are harmful. A sample of the suspension so obtained is cultured aerobically and anaerobically; the remainder is stored either at 4° C. for 12–24 hours or at −79° C. for longer periods.

Short-term culture of a sample of the cell suspension can be carried out at this stage using Lajtha's (1954) method, and this will give an indication of the activity of the cells—for example, their capacity to synthesize nucleic acid (D.N.A.). Unfortunately no method has yet been discovered of increasing the yield of useful cells by long-term culture.

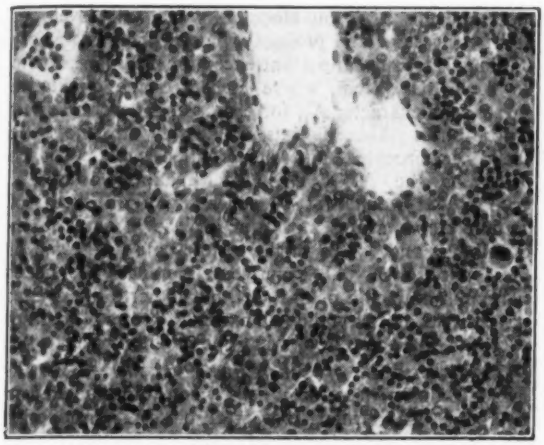

FIG. 3.—Foetal liver at 18 weeks. A megakaryocyte can be seen on the right. (×160.)

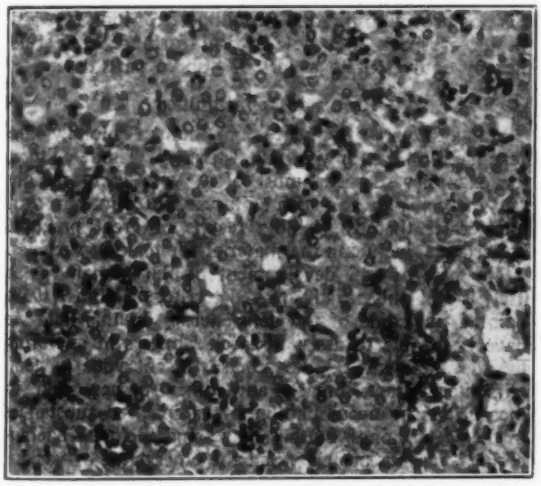

FIG. 4.—Foetal liver at 28 weeks. Only islands of darkly staining haemopoietic cells remain. (×160.)

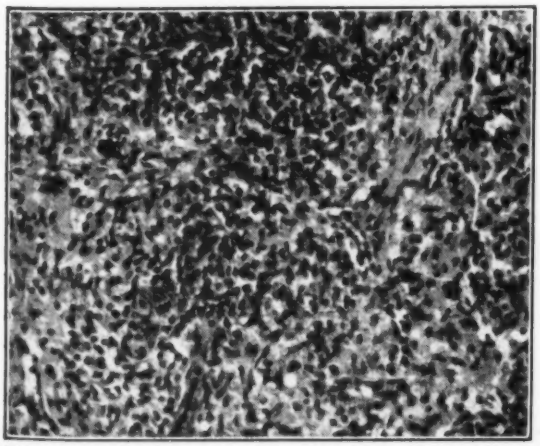

FIG. 5.—Foetal spleen at 20 weeks. An incompletely formed follicle and a few islands of haemopoiesis are shown. (×160.)

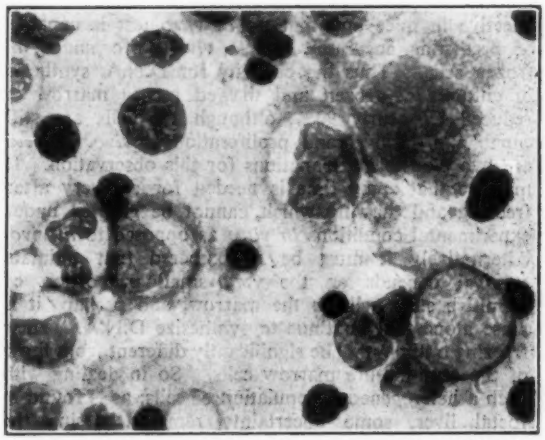

FIG. 6.—Smear of foetal liver and spleen suspension. Myeloid, erythroid, and undifferentiated stem cells can be distinguished. (×608.)

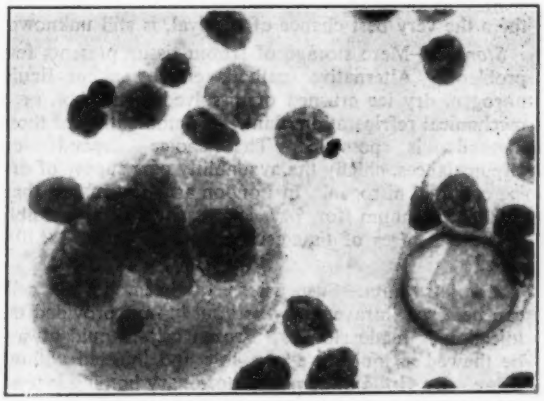

FIG. 7.—Smear of foetal liver and spleen suspension to show megakaryocyte. (×608.)

Freezing and Thawing of Cells

Long-term storage of frozen cells is no longer a novelty. The work of Parkes and others, and, in particular, their discovery of the protective action of glycerol, has enabled many different types of cells to be preserved for months or years at the temperature of dry ice (−79° C.) or liquid nitrogen (−195° C.). But there is still ignorance of some of the principles involved.

Thus, in the case of spermatozoa, about which most is known, there is a wide variation in freezing optima from one species to another (Polge, 1957). For the rabbit 25–30% glycerol in buffered glucose is best, compared with 10% glycerol in glucose + egg yolk for the stallion; 10% glycerol is also the optimum for bull semen, but for man the concentration should be 0–5%. For the ram no good method has yet been discovered, and, although thawed raw spermatozoa may be actively motile, their fertility is always severely reduced. As well as these species variations there are undoubtedly different optima for different tissues within the same species and for cells of one tissue at different stages of maturation.

The standard preserving medium for bone marrow is 15% glycerol in serum, but there is no proof yet that this is the optimum for man as it probably is for the mouse. Ferrebee *et al.* (1957), for example, have shown that lower concentrations of glycerol are almost equally effective in mice and that no *in vitro* test is capable of predicting accurately the *in vivo* performance of frozen cells. Thus the capacity for D.N.A. synthesis in cultures of frozen and thawed mouse marrow is reduced by nearly 90%, although the cells are still capable of survival and proliferation *in vivo*. There are two plausible explanations for this observation. It may be that some time is needed for recovery after freezing and thawing which cannot be granted under experimental conditions *in vitro* as opposed to *in vivo*. Alternatively it must be remembered that ultimate survival depends on the very small proportion of primitive stem cells in the marrow, and perhaps it is these alone that continue to synthesize D.N.A. Their freezing optima may be significantly different from those of the semi-mature marrow cells. So in dealing with such a heterogeneous population of cells, as is found in foetal liver, some uncertainty remains. Using the technique of autoradiography, we can show that D.N.A. synthesis continues after freezing and thawing in 15% glycerol-serum, but what proportion of the all-important stem cells have survived, and whether we have given them the very best chance of survival, is still unknown.

Storage.—Mere storage of frozen tissue presents few problems. Alternative methods employ either liquid nitrogen, dry ice crushed or dissolved in alcohol, or a mechanical refrigeration plant. A combination of these methods is possible. The choice depends on circumstances, chiefly the availability of a supply of dry ice or liquid nitrogen. In London at a cost of less than £100 per annum for dry ice it should be possible to store 5 litres of tissue-suspension or about 3×10^{12} cells.

Administration.—Suspensions of haemopoietic cells can be given intravenously without hazard provided the injection is made slowly. Frozen cells should always be thawed as quickly as possible and injected without delay. By virtue of some extraordinary homing instinct it has been shown experimentally that cells so administered find their way to the appropriate site in the body, where they settle and multiply.

Some Properties of Foetal Cells

Foetal Blood Groups.—Contrary to general belief, most antigens of foetal blood cells are well developed at an early stage and probably, indeed, from their very origin. The only important exception to this seems to be the ABO system, where there is some qualitative defect; the character A_1, for example, is never manifest before birth. There is thus no difficulty in genotyping foetal erythrocytes, and our routine practice is to determine the ABO, D,C,E,c,e,M,N,S, Fy^a, and K groups. It would not be surprising if an excess of certain blood groups was found, since incompatibility of mother and foetus might be the cause of some of these abortions. ABO antigen differences are under particular suspicion of this sort, but hitherto our figures have revealed, if anything, an excess of group O foetuses—that is, the opposite of what one might expect.

Transplantation of Other Foetal Tissues.—There is evidence that certain foetal cells, when transplanted, can overcome the normal homograft barrier. Endocrine glands have received most attention, and many believe that parathyroids, at least, can survive and function in their new host (Jordan, Foster, and Gyorkey, 1958). If this was proved to be so, we could perhaps look forward to the prospect of a new radical form of endocrine therapy equivalent to a sort of "spare parts" service.

Research Opportunities

Many forms of research in human biology are dependent on a supply of foetal tissues. Tissue culture, for example, succeeds most often with early rapidly growing cells, and on such cultures viruses may in turn proliferate, thereby yielding results of great practical importance, including the material for making vaccines.

The growth and development of the human foetus itself is still only a half-charted territory; Willis (1958) pointed out some of the deficiencies. In this field we have been able to assist research workers in exploring the development of the lungs, the nervous system, alimentary tract, breast, and other tissues, and in measuring the accumulation of radioactive substances in the foetal bones. Others have studied foetal haemoglobins, plasma proteins, and the emergence of various enzyme systems.

If so little is known of the normal human foetus, what of the abnormal? Only isolated descriptions are available of the early stages of many abnormalities. We may hope in time by careful search to discover specimens of deformities—for example, hare-lip—at a stage nearer to their origin, whence there could be derived information of use in treatment or even prevention.

Firstly, of course, we are indebted to all who have helped to provide us with foetuses. This work has latterly been supported by a grant from the Medical Research Council, and we must acknowledge the recent assistance of Dr. G. Barraclough. We also thank Mr. K. G. Moreman for the photomicrographs.

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Reports of Societies

"CALAMITY SYNDROME"
A NEW CLINICAL ENTITY

[FROM A SPECIAL CORRESPONDENT]

At a meeting of the Section of Psychiatry of the Royal Society of Medicine on February 10, Professor MARTIN ROTH, of Durham University, described what he believes to be a hitherto unrecognized clinical entity. He calls it the "phobic anxiety-depersonalization syndrome." Afterwards two colleagues, Dr. ARTHUR KING and Dr. J. C. LITTLE, gave a preliminary report on its treatment.

Precipitating Factors

At two departments of psychiatry attached to general hospitals, Professor Roth and his colleagues have, since 1956, studied 135 cases presenting with depersonalization. There were 93 women and 42 men, of mean ages 35 and 38 respectively, he said. They had investigated the family background, childhood development, premorbid personality, and the mode of onset of the illness, using as controls a group of 50 neurotics without depersonalization and another of 42 physically ill patients from the same hospital. The illness had followed closely on bereavement or a sudden and serious illness in a close relative or friend (37%), illness in or acute danger to the patient himself (31%), and quite often severance of family ties or acute domestic stress (15%). Thus in some 83% of the cases the illness had attended circumstances of a painful or disastrous nature, usually of an acute kind. As a factor, illness appeared to be more important in men and bereavement in women. Of considerable interest was the frequent association of the onset in the remaining cases with an accidental or induced change in the level of consciousness, often of a slight or transient character and associated, for example, with faints, light anaesthesia, or trivial injuries.

In just under a half of the cases the "calamitous precipitants" just described had impinged on a person already "sensitized" to their impact by existing diffuse anxiety which had usually been present for some weeks or months. Professor Roth emphasized, however, that the new phase of depersonalization in such patients had the novelty of a metamorphosis and was not merely an intensification of the pre-existing anxiety.

Depersonalization and Phobic Anxiety

Describing the clinical picture of the developed illness, Professor Roth said that almost invariably associated with depersonalization was a characteristic pattern of phobic anxiety—fear of being alone in the streets, of entering crowded rooms, of having to wait, and so on. Conversely he had found that only a small proportion of cases with phobic anxiety were free from depersonalization feelings of an episodic or chronic nature. To him, these two conditions seemed to be at present inseparable. The depersonalization and phobic features might commence immediately after the trauma or merge insensibly with a phase of clouding or of hysterical conversion symptoms. Hysterical conversion symptoms were common at the onset and not infrequent in the chronic stage, and the same held true of disturbance of consciousness. In fact one-third of the total suffered from feelings of faintness, giddiness, or one or a succession of actual faints, and in this respect differed significantly from the group of mixed neuroses. He thought that in this syndrome we were dealing with a "pan-neurosis," so that a high proportion of the cases, in addition to their symptoms of depersonalization and phobic anxiety, suffered also from one or more features of tension and vasomotor disturbance, reactive depression, hypochondriasis, hysteria, or very mild obsession.

Almost 10% presented with the picture of endogenous depression, and, although the association of endogenous depression with depersonalization had often been described, he did not believe that these two conditions had a common origin. The poor results with electric convulsion therapy in their cases seemed to bear this out. A few of the cases had presented with features suggestive of schizophrenia, but he believed that here they were dealing with a relatively benign condition on the borderlands of schizophrenia and allied to such conditions as the amphetamine psychoses and those induced by hallucinogens. A significantly high percentage of cases displayed symptoms suggestive of dysfunction of the temporal lobes, and, for example, the "private cinema phenomenon" was of great interest aetiologically as it had been described in pre-delirious states.

Previous Personality

With regard to previous personality, on the one hand these patients were conscientious and scrupulous and generally mildly obsessional, while on the other they were judged to be dependent and emotionally immature to a marked degree. So far as their development was concerned, they tended to live in a restricted social milieu bounded by the family, betraying little sign of maladjustment before the onset of their illness other than by mild childhood phobias, slightly more physical ill-health than is found among the general run of people, and, very interestingly, a high incidence (60%) of total frigidity among the women. This last was present despite above-average success in, and thus perhaps a greater drive towards, finding marriage partners. The proportion of failed marriages, although higher than in the normal controls, was lower than among the other neurotics, but the differences were not significant. The evidence suggests that the women seek marriage for security and strive to maintain their marriage ties although rarely attaining adult patterns of sexuality.

Psychopathology

Discussing their findings, Professor Roth said that purely psychological theory, whether couched in analytic terms or in the form of learning and conditioning theory, did not adequately explain the clinical picture. These states bore some resemblance to the "fright neurosis" of the first war and the "traumatic neurosis" of Kardiner. Kardiner believed that the initial symptoms in that condition were physiogenic in origin, but he found unconvincing Kardiner's view that these neuroses were kept alive by motivation or unconscious psychological needs, nor did he believe this was the case with the syndrome under review. The only way in which depersonalization could be evoked at will was by taking hallucinogenic drugs or by stimulating the temporal cortex, each of which involved a change in the level of awareness, however subtle. When, as in the phobic anxiety depersonalization syndrome, there were phenomena which ran the whole gamut of temporal lobe symptomatology, and were associated with a chronic disturbance of attention and involved in addition the hazard of loss of consciousness, he believed that we were dealing with some chronic disturbance of the mechanisms that regulate awareness; and that in these states we saw one of those step-like gradations of consciousness with which, at deeper levels, we were familiar in the patterns of delirium and irreversible coma. Such a hypothesis had the merit of integrating the three modes of onset of the condition—calamity, physical illness, and fainting or anaesthesia. The condition was a true psychosomatic disease.

Finally Professor Roth made brief reference to the electroencephalographic and biochemical studies on these cases which were in progress. About one-third of 60 patients examined by E.E.G. had been found to have abnormal

records, mainly excess theta activity, and a few showed medium voltage activity in the temporal areas and posterior part of the head. The differences from a control group of reactive and endogenous depressions were not significant. Preliminary reports of the biochemical investigations showed that the level of catecholamines, especially of noradrenaline, seemed high before treatment and fell markedly afterwards.

Thiopentone Abreaction

Dr. ARTHUR KING (with Dr. J. C. LITTLE) gave a preliminary report of the treatment of the syndrome with thiopentone. Their first experiments with thiopentone abreaction had been prompted by its reported effectiveness in the treatment of war neuroses and by subsequent references in the literature to its use in depersonalization states. After some time it became clear that in many of their cases abreaction was difficult or impossible to provoke and that it was apparently unnecessary for a good result. They had therefore devised a technique which involved the administration of 2.5% thiopentone intravenously at a rate sufficient to produce progressive sedation and light sleep in about 15 minutes. No attempt was made to effect abreaction, and psychotherapy was confined to discussion of concrete problems, simple reassurance, and the provision of a simple formulation of the illness as a response to personal calamity. The patient was allowed to awake spontaneously, this occurring in about 5 to 10 minutes. Abreaction, if it did occur, was of no special prognostic significance. They found the best spacing for the treatments was two or three times a week. In successful cases benefit was cumulative, beginning after three or four treatments. If benefit was not apparent after six treatments, it seldom occurred thereafter. There was no advantage in giving more than ten treatments. Improvement continued after completion of the course, the greatest benefit being apparent about three months afterwards.

Dr. King then presented the results, in a controlled trial, of this treatment in a series of patients with phobic anxiety depersonalization states. While stressing that the results of this initial trial must be interpreted with reserve, he said that it had been most encouraging to find a figure of 85% improvement three months after treatment, particularly in relation to a condition which was generally regarded as intractable. He believed that the therapeutic process was merely triggered by a course of thiopentone and was thereafter self-perpetuating. It was possible that the essential therapeutic process was an effect on the mesodiencephalic reticular systems controlling consciousness. Conceivably the thiopentone acted by altering the activity of the adrenergic arousal system, whose functional abnormality might lie at the core of the "calamity syndrome." This hypothesis received some support from the preliminary results of catecholamine estimations on the urine of treated cases and to a lesser extent from the E.E.G. studies.

The Tobacco Manufacturers' Standing Committee has produced a bibliography on *The Constituents of Tobacco Smoke*, edited by H. R. Bentley and E. G. N. Berry. It lists references to published papers, and groups them under such headings as "Nicotine," "Hydrocarbons," "Arsenic," and so on. The bibliography is not necessarily complete, nor is it intended to be a critical review. It is issued from 6–10, Bruton Street, London, W.1.

FIG. 1.—Head and shoulders from Reynolds's finished portrait of John Hunter. From the photograph taken in 1957 by the Courtauld Institute of Art.

Nova et Vetera

REYNOLDS'S TWO HEADS OF JOHN HUNTER

A LEGEND DISPROVED

Sir Reginald Watson-Jones described, in his Hunterian Oration before the Royal College of Surgeons on February 16, the fascinating discovery which he has made concerning Reynolds's "second thoughts" in his famous portrait of John Hunter. The history of this portrait will be given in detail in the Catalogue of the College Portraits about to be published by Messrs. Livingstone of Edinburgh. It is sufficient here to recall that the portrait belonged to Hunter's widow and son till they gave it to the College in 1817. Sir Joshua Reynolds painted and exhibited it in 1786, but recorded in his diary that Hunter sat to him again in 1788 and 1789 for a retouching of the same canvas. The portrait has been cleaned at least five times since then, and was most skilfully restored by Dr. Johann Hell in 1954 (Fig. 1). With the approval of the President of the College and the expert advice of Mr. F. I. G. Rawlins, scientific adviser to the National Gallery, Sir Reginald has now submitted the painting to *x*-ray examination.

His intention was to prove or disprove an old legend. Drewry Ottley, in the first full-length life of Hunter,[1] tells the following story.

FIG. 2.—Reynolds's original under-painting. As shown by *x*-ray examination at the National Gallery in 1959.

"Reynolds found Hunter a bad sitter and had not been able to satisfy himself with the likeness, when one day, after the picture was far advanced, Hunter fell into a train of thought, in the attitude in which he is represented in the present portrait. Reynolds without saying a word, turned the canvas upside down, made a fresh sketch, with the head between the legs of the former figure, and so proceeded to lay on over the former painting the colours of that which now graces the walls of the College."

This was written 40 years after Hunter's death; now Sir Reginald's investigation has disproved this legend. There is no indication of earlier legs at the top of the picture, nor an earlier head at the foot. But he has made a most interesting discovery. Reynolds did paint Hunter's head twice, though without inverting his canvas. The *x* rays reveal a complete first painting of the head (Fig. 2) underlying the completed head but not agreeing with it in contour or detail. Sir Reginald and Mr. Rawlins are satisfied that the final head, still seen by the naked eye, is Reynolds's work and not the rehandling of a restorer. Sir Reginald argues cogently that the earlier head and face, now visible by *x* rays, show Hunter as he was in 1786, while the finished portrait shows us what Reynolds saw at Hunter's last sitting in 1789—a face thinned and distorted by illness, with the eyes slightly convergent. This would accord with Hunter's own account of the nervous and sensory troubles which he underwent.

W. R. LEFANU,
Librarian, Royal College of Surgeons of England.

REFERENCE

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AN EARLY PSYCHIATRIST

JOHANN CHRISTIAN REIL: BORN 1759

The dominance of Freud in the field of psycho-analysis tends to obscure the work of his great predecessors. One of them, Johann Christian Reil, had in his day and age a pervasive influence on literature and society.

Born on February 28, 1759, at Rhaude in Eastern Friesland, Reil was originally destined for the Church, but a distaste for theological studies, fostered by an increasing interest in the natural sciences, led him to the University of Göttingen, where he studied medicine. Finding the atmosphere very restrictive, he moved to Halle, where, under P. F. T. Merkel (1756–1803) and J. F. Goldhagen (1742–88), he graduated in 1782 with a thesis on the yellow humour in the blood. Returning to Eastern Friesland, he practised for five years before being recalled to Halle, where in 1788 he succeeded Goldhagen as professor of therapeutics and director of the chemical institute.

Reil was an active observer of the psychiatric factors in illness. In the *Archiv für die Physiologie*, which he started in 1795, he outlined in an article of some 150 pages his belief that "vital force" was explicable in physical terms. Fevers attracted him, and his *Erkenntniss und Cur der Fieber* (1799–1815) outlined his theory that they arose as a result of irritability of a part of the system, especially the blood vessels or the nerves. Watching fevered patients in delirium sharpened his interest in the psychiatric causes underlying illness, and in 1805 he founded with a colleague, Kayssler, the *Magazin für die psychische Heilkunde*—probably the first psychiatric journal in the world. It ran for three numbers and was followed by the *Beyträge zur Beförderung einer Kurmethode auf psychischem Wege*, which appeared in 1807. As an ancillary interest Reil took up the use of the cold bath in fevers. A bathing institute was established in Halle, where brine, shower, douche, and Russian baths were given.

Reil impressed his contemporaries. Goethe, one of his patients, noticed that Reil observed him for a fortnight without prescribing any more than a palliative. After the battle of Leipzig, Reil was made director-general of the hospitals established in Halle and Leipzig, to cope with the wounded. He died of typhus after a month, on November 12, 1813.

The finest statement of his psychiatric views is given in the *Rhapsodien über die Andwendung der psychischen Curmethode auf Geisterzerrüttungen* (1803). As its title implies, it was a descant on the application of psychotherapeutic principles to mental disorders. Reil was aware of the integrated personality of individuals and the lack of this integration exhibited by his abnormal patients. Fantasy, dreams, and other escape mechanisms from the outer world he approached in a spirit of humility, firmly insisting, however, that they should be treated both through the body and

through the mind. He rejected blood-letting, purgatives, emetics, and drugs, to explore psychiatric cures known to the Greeks, the Romans, and the Arabs. He was convinced that the secret of successful treatment was to eliminate obsessions. To do so he stressed that asylums should afford plenty of opportunities for fresh air and exercise. To him they should not be prisons but hospitals for nervous diseases or psychiatric centres. And as such, he argued, they should not be built in a massive barrack block but as a cluster of small buildings.

Though published two years after Pinel's *Traité médico-philosophique sur l'aliénation mentale*, Reil's book is a classic on its own. Max Neuberger, in an account of Reil's life and writing which he published at Stuttgart in 1913 to mark the centenary of Reil's death, called it "one of the most worthwhile books in the literature of the subject." It is to be hoped that one of the many medical historians now at work will give us an authoritative English biography of this interesting and important man. Since Reil's time we have had two interesting German studies by Dr. L. Mueller, *J. C. Reil und die Romantik* (Würzburg, 1935), and Arnold Boldt, *Über die Stellung und Bedeutung der Rhapsodien . . . in der Geschichte des Psychiatrie* (Berlin, 1936). Can we some time have an English study, placing his work in its proper perspective? After all, there are over 20 dissertations (for which he acted as *praeses*) published and available at the British Museum.

W. H. G. ARMYTAGE.

HUNTERIAN SOCIETY ORATION

On February 23 Sir ARTHUR PORRITT delivered the Hunterian Society Oration at the Mansion House. His subject was "John Hunter's Women."

John Hunter's well-proved idealism, his breadth of vision, his inherent simplicity, his love of nature, his very lack of the social graces, his isolation in his work, said Sir ARTHUR, all seemed to indicate facets of his character that might well have been influenced by or appeal to the women around him.

John Hunter's Wife

The Orator then discoursed upon certain of John Hunter's womenfolk: Hunter's mother and sisters, his wife and daughters, and his nieces. Of Hunter's wife, Anne Home, Sir Arthur said:

"Without Anne Home, most certainly the story of John Hunter would have been a very different one and, most probably too, the development of modern surgery, in so far as it stems from John Hunter's work, would likewise have been materially affected. This may seem a didactic statement and to give too great an emphasis to his wife's influence. But, despite the many facts known about her and recorded in sporadic phrases by many of Hunter's biographers, her personality as a whole and its effect on her husband would seem never to have been considered in perspective.

"Her arrival on the Hunterian scene was the dividing line between Hunter the anatomist and Hunter the surgeon. Before their marriage, she had decided that her husband-to-be must be an established surgeon, must be attached to a hospital staff, and must have a reputable surgical practice. She was thus the spur and the incentive—almost the goad—that stimulated John Hunter at a critical period of his career. Like many very beautiful women, she was not perhaps really so feminine, but she had a longing for fame and social standing—her revolt against anonymity.

"No two personalities could have been more different, and yet there was a reciprocity between them which made their

(Continued at foot of next column)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Saluric (Merck Sharp and Dohme).
Warduzide (Ward Casson).

These are preparations of chlorothiazide, which is much the most valuable oral diuretic available at present. Its administration causes a considerable diuresis of sodium chloride and water and a smaller increase in the excretion of potassium and bicarbonate. The mode of action of the drug is unknown. Its continued use does not lead to the production of a metabolic alkalosis, such as may be encountered during mercurial therapy, nor of a metabolic acidosis of the type produced by acetazolamide; and, possibly because of this, patients rarely become refractory to its diuretic effect. It would appear to be almost as effective as the parenteral mercurial diuretics in the treatment of cardiac, renal, and hepatic oedema and in the management of pre-eclamptic toxaemia, and, being given by mouth, is a much more convenient preparation for the patient. Its administration to patients with advanced hepatic cirrhosis has occasionally precipitated hepatic coma, and it is best avoided in cirrhotics with a history of the neuropsychiatric symptoms of hepatic insufficiency. It may also be employed to potentiate the effect of hypotensive ganglion-blocking agents such as mecamylamine. Thrombocytopenia and, more rarely, agranulocytosis have been reported after administration of the drug (Zuckerman, A. J., and Chazan, A. A., *Brit. med. J.*, 1958, **2**, 1338; Nordqvist, P., *et al.*, *Lancet*, 1959, **1**, 271).

The usual daily dose is 1–2 g. As in the case of mersalyl, the drug should be given intermittently for one or two days at a time at weekly intervals. The ability of this drug to produce potassium depletion has been insufficiently stressed, and severe depletion is readily produced by continuous administration to patients on diets low in sodium unless they have potassium supplements. 2 to 6 g. potassium chloride per day will usually prove to be sufficient to maintain the patient in reasonable potassium balance when the drug is used intermittently.

N.H.S. basic price: saluric, 100 tabs. 0.5 g., 47s. 6d.; warduzide, 100 tabs. 0.5 g., 42s. 9d.

(Continued from preceding column)

combined lives both successful and happy, whilst it in no way fettered their individual activities and pursuits. Their marriage was due to an odd mutual fascination, founded on an appreciation of each other's inherent talents and strong enough to subdue, at most points, their obvious differences in temperament. The turning-point in John Hunter's life—from the unruly boy, the rather lost but seeking youth, the incredibly hard-working anatomical apprentice, to the rugged, astute, self-opinionated, and *still* incredibly hard-worked and hard-working surgeon—came after his years of military service, but the metamorphosis was due to Annie Home. To John Hunter she provided all the answers to the attributes he had not got, and knew by then he could not himself acquire—culture, the arts, the social graces, the ability to mix with people—and the *right* people.

"Whilst in no way altering his predestined course, she deviated and widened his objectives. And, beyond this, there was a Scottish mystic element in his affection for his wife which showed that, under the rough, almost coarse, exterior of John Hunter, was a softness and a sentimentality that do much to increase one's feelings for the hard-bitten scientist. Anne Home stimulated his hidden humanities—she proved that there was a soft and vulnerable under-belly to the armadillo. To her, we probably owe more to-day than we have to date appreciated."

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Future of the Tuberculosis Service

SIR,—In your leading article on the Joint Tuberculosis Council's *Report on the Future Service for Tuberculosis and Diseases of the Chest* (*Journal*, January 31, p. 286) you recommend that consideration be given to the closure of chest hospitals and sanatoria situated in rural areas and the building of chest units in the purlieu of general hospitals. General hospitals are of course usually situated in the centre of towns and cities. There is a certain connexion between atmospheric pollution and chest disease. Before deciding to liquidate first-class beds situated in green belts and rural areas it might be as well to consider the pathological status of some of the patients to be treated.

In the treatment of chronic bronchitis I have been able to observe the difference in results which can be obtained when such patients are treated in general medical wards and under modified sanatorium conditions in the country. The antibiotics achieve their temporary effect under both conditions, but the patient receives a more lasting benefit and stability under the latter. Asthmatics do not thrive in busy chest wards *vis-à-vis* respiratory failures. They are better treated in the tranquil cubicles of the rural sanatoria. Restoration of morale under good atmospheric conditions, a cheerful environment combined with sound physiotherapy and graded exercise, can even help advanced cases of emphysema. Perhaps readmission may be required the following winter, but experienced sanatorium staffs are not unaccustomed to relapse, and many respiratory cripples have more faith in environment than tetracycline.

A surgical colleague has assured me that cases of renal tuberculosis do far better under "sanatorium" than hospital conditions. I have been told, by those in a good position to know, that patients with peptic ulcers get worse in busy general wards, and I have been asked to treat them in the relative peace of rural sanatorium beds. A gastro-enterologist has asked me to treat his cases of ulcerative colitis away from the comparative turmoil of his general hospital milieu. A cardiologist would have me admit his recovering cases of coronary thrombosis to the controlled and experienced regime of graded mobilization obtainable in sanatoria.

It is strange, Sir, that some of my colleagues profess to regard the sanatorium as unsuitable for the treatment of pulmonary tuberculosis, and demand that new units (or even old dumps) should be used for this purpose under their personal care. In the headlong flight from an essential specialty to integration with general medicine, it is to be hoped that conditions of service for doctors will not always prejudice conditions of treatment for patients.—I am, etc.,

Harefield Hospital, Middlesex. L. E. HOUGHTON.

Immunization Programmes

SIR,—Dr. M. Adams and his colleagues (*Journal*, February 7, p. 362) have suggested an immunization programme and asked for criticism of their scheme. Theirs is only one of many schemes which have been proposed in theory or put into practice. Last year, my colleagues and I (*Journal*, January 4, 1958, p. 39) drew attention to the confusion that exists on this subject, and put in a plea for a national policy. If these schemes are to be discussed it seems to be worth considering their aims.

The first and obvious aim to-day is to immunize as many infants as possible against whooping-cough, diphtheria, poliomyelitis, tetanus, and smallpox. The second aim is to give the various injections early enough to protect the young infant, yet not so early that antibody formation is likely to be incomplete. The third aim is to give the injections in the form least likely to injure the child.

In practice this means giving whooping-cough immunization very early, as Dr. E. C. H. Huddy suggests (*Journal*, January 31, p. 303), but it may mean delaying immunization against diphtheria and smallpox[1] until the age of 6 months; and it means that there is an added danger of precipitating poliomyelitis if certain vaccines are combined.

Scientifically, then, the ideal scheme must be one in which the antigens are given singly, and not in combination. This at once avoids the added risk of poliomyelitis inherent in combined vaccines, and allows one to choose the optimum age for each immunizing agent. There might be some argument about the exact order, but probably it would be whooping-cough first, then poliomyelitis, smallpox, diphtheria, and tetanus.

Why, therefore, should there be any question of combined vaccines at all? The answer, of course, is: (1) To reduce the number of attendances imposed on infants and parents. (2) To reduce the amount of injection-induced terror of doctors that the infants are likely to acquire. (3) To simplify the scheme so that everyone does not get into a hopeless muddle about what injections have been given, and what injections are yet to come. There is no doubt that the simpler the scheme the more likely it is to be completed in the greatest number of children. From these points of view the ideal would be to give all the immunizing agents together in the smallest possible number of injections, if that were feasible, and get the whole thing over as quickly as possible.

Now the first thing is to decide whether or not these considerations are sufficiently important to modify the scientifically ideal programme of immunization. Personally, I think they are, and I think there must be some combination of vaccines, but this means that there must be a compromise between a socially desirable scheme and the scientific ideal. It is probably impossible to use combined vaccines, and yet to give all the immunizing agents in the safest form at the ideal time for each and every one. Unless the nature of this compromise is clearly realized there is bound to be a lot of fruitless discussion on immunization programmes. If the necessity for compromise is accepted, then the only argument is how many antigens can be combined to give a reasonably safe and efficient vaccine, and what is the best age to give it.—I am, etc.,

Wantage, Berks. I. S. L. LOUDON.

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The Influenza Epidemic

SIR,—We wonder if this epidemic of so-called influenza really is influenza. We notice that, unlike the previous epidemics, whole families are affected at the same time and not one after the other; also there is a high incidence of frontal headaches, pains in the chest (usually left side), pleuritic in type, and high fever 103–104° F. (39.4–40° C.) and abdominal discomfort, with diarrhoea in some cases and more frequent relapses.

These signs suggest to us that this is an epidemic suggestive of Bornholm disease.—We are, etc.,

R. G. WIGODER.

London, S.E.6. H. G. JEFFS.

Lumbar Puncture

SIR,—Your leading article on lumbar puncture (*Journal*, December 20, p. 1520) and the subsequent correspondence (January 3, pp. 48 and 49) bring to mind an unforgettable experience as a newly qualified houseman. I hope its description may help others in a similar position.

A girl, aged 3 years, had been an in-patient for some time with tuberculous meningitis and had severe headaches. These had been relieved by withdrawing a small quantity of C.S.F. by lumbar puncture: the manœuvre had habitually been done with caution, as she had markedly raised intracranial pressure, though with no suggestion of a blockage.

On this occasion about 4 ml. was slowly run off over about five minutes and a nurse observed the patient's pulse and respirations throughout: the needle was withdrawn and all seemed well, but half a minute later she was observed to be pale, apnoeic, and pulseless. A 5-ml. hypodermic syringe was used to draw up the withdrawn fluid, and the fluid was immediately reinjected into the theca. The results were dramatic: almost immediately the colour improved, the pulse became palpable, and the breathing recommenced: unfortunately, so did the headache.

The surprising thing at the time was the delay in onset of what was presumably a "pressure-cone" phenomenon: although not very great, it was almost enough for the instruments to be tidied away and the trolley removed; had this occurred, the delay in reintroducing the C.S.F. might have proved fatal.—I am, etc.,

Aldershot. A. J. McM. CAVENAGH.

When to Tie the Cord

SIR,—Dr. E. D. Burnard's article on "The Cardiac Murmur in the Newborn" (*Journal*, January 17, p. 134) set me thinking and asking questions, particularly, What is the modern teaching on the time to tie the umbilical cord? My investigation was so instructive that I think it may interest your readers and, I hope, perhaps lead to some agreement on this not unimportant topic.

The *Queen Charlotte's Textbook of Obstetrics* would not agree with this assessment, for it does not list it in the index and just states[1] that the cord should be divided "about 4 in. (10 cm.) from the umbilicus." Gibberd[2] is emphatic that "there is nothing of value to be gained by delaying the division of the cord until it has stopped pulsating," but Eden and Holland[3] are not so sure, as they say, "The cord may be divided as soon as it has ceased pulsating, or earlier when respiration has been satisfactorily established." Johnstone and Keller's *Textbook*[4] is a bit more definite still: "Wait for a few minutes until the cord shows signs of ceasing to pulsate." Roques[5] states: "It is debatable whether the cord should be tied immediately, or delayed until cord pulsation has ceased," and gives five lines of discussion. Strachan[6] gives a much fuller discussion of the subject yet reaches strangely contradictory conclusions. He is very emphatic about the need to prevent loss of blood from the cord because "the newly born infant stands the loss of even the smallest amount of blood very badly," yet a few lines below quotes Wilson *et al.* that "immediate ligature of the cord results in the retention of fully 100 c.c. of blood, or about one-third of the blood volume of the new-born child, in the placenta." He mentions that depriving the infant of this blood must deprive it of a substantial reserve of iron—the point which was, I think, first made by Sir Joseph Barcroft—but says that he has followed babies carefully and could find no difference between those who had had the cord tied early and late, and concludes, "This is therefore an entirely theoretical consideration of no practical importance." These are almost the identical words used at the Glasgow B.M.A. meeting when I suggested on theoretical grounds that it was not a good thing to warm up a person suffering from the shock of coronary thrombosis, and I hope this letter may have a similar effect to the one in which I related that incident.[7]

Greenhill[8] has a stimulating discussion but draws no definite conclusions. I got much of the information I sought from Gunther.[9] She shows, what I had suspected, that the caesarean baby, by reason of the immediate clamping of the cord, has less blood than one born normally. She also points out that raising the baby above the abdomen actually lets blood drain back into the placenta. This seems one reason why caesarean babies do less well than normal ones. "The [neonatal] mortality of caesarean section, however, continues to be about double that of all patients delivered" (Douglas and Stromme[10]). As one of the reasons given for this is that these babies are underweight, it seems strange that the loss of about 100 ml.—that is, some 3 to 4 ounces—is commonly overlooked. Even Barcroft,[11] who showed little interest in clinical medicine, wrote: "Is it right that according to the constitution of the baby and the fashion in clamping the cord there should be a difference in the blood volume ranging from 72 c.c. per kilo to 149 as between one baby and another, or a difference ranging between 37 c.c. and 83 c.c. in the corpuscle volume. Has not God made babies more nearly after His own pattern, or at all events after some more uniform pattern than that!"

I nearly wrote that this matter is universally overlooked, for ligature of the cord is not referred to at all by Bourne and Williams,[12] and Franklin,[13] reviewing "Recent Changes in the Care of the Newborn," discusses care of the cord with no reference to when it should be tied. Similarly Chassar Moir,[14] describing caesarean section, merely says that the cord should be divided and the baby handed to the assistant; but finally I found in Beck's *Obstetrical Practice*[15] a really full consideration of the matter. This is a massive American tome, though published in England, but it does give value for weight. *Inter alia* he says: "If the umbilical cord is not clamped at once, 50 c.c. of the blood in the placenta is returned to the child in the first minute and about 100 c.c. in about thirteen minutes. Because this blood is extremely valuable to the newborn child (especially if it is born prematurely) haste should be avoided in ligating the cord," and later on, when describing caesarean section,[2] he recommends that the placenta should be removed with the baby attached and suggests that it should be suspended above the infant in a towel to let the blood in it drain into the baby. This at least shows that on the other side of the Atlantic obstetricians are becoming alive to the problem, and one cannot help thinking that for the student at least some greater uniformity in the teaching of British obstetricians would be an advantage. And from the point of view of truth and the health of the child it is desirable that this unanimity should not be reached from pride or prejudice in the Royal College of Obstetricians and Gynaecologists but from full consideration of the facts.

This letter is so long that I have no space for the points I wished to raise when I set out on this investigation, but two final remarks seem pertinent. The main reason for the immediate ligation of the cord coming into vogue was the hope that by such means the fatal type of jaundice might be prevented, being then put down to the haemolysis of the extra blood instead of the then unknown blood-group factors. The main reason now advanced in the textbooks for this procedure is to avoid chilling of the infant, although Burnard and Cross[16] have shown that babies with asphyxia normally have a reduced rectal temperature and add "the lower temperature may have survival value." Obstetrical teaching in these days should not be based on plausible assumptions but on an appreciation of physiological and anatomical data, for as Dawes

et al.[17] conclude it is "unwise to attempt any prediction [about neonates], based on experience in adult animals, without further experimental observation."—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

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Case Reports from the Bible

SIR,—The very interesting article "Noah—An Albino," by Professor Arnold Sorsby (*Journal*, December 27, p. 1587), suggests another biblical question that could also, perhaps, be answered scientifically: What was the snake that bit Saint Paul on the Island of Melita?

In Chapter 28 of the *Acts of the Apostles*, describing Saint Paul's shipwreck on the Island of Melita (or Malta, to give it its modern name), the following account can be read:

"And when Paul had gathered a bundle of sticks, and laid them on the fire, there came a viper out of the heat, and fastened on his hand. And when the barbarians saw the venomous beast hang on his hand, they said among themselves, No doubt this man is a murderer, whom, though he hath escaped the sea, yet vengeance suffereth not to live. And he shook off the beast into the fire, and felt no harm. Howbeit they looked when he should have swollen, and fallen down dead suddenly: but after they had looked a great while and saw no harm come to him, they changed their minds, and said that he was a god."

From the above description, a very probable determination of the genus of snake concerned can be made. It was certainly not a viper—the only genus of venomous serpents for most of the European continent, including the Malta area. None of these will attack if it can save itself by flight. Nor, having bitten, could it hang on long enough to be shaken off into the fire as mentioned.

The snake that best fits the picture is the poisonless, but poisonous-tempered, *Coluber viridiflavus* Lacepéde, which will attack on little or no provocation and will even pursue human beings when irritated. After biting, it will sometimes hang on like a bulldog, as it possesses a number of sharp teeth in each jaw. A very similar species, *Coluber jugularis caspius* Gmelin, is fairly common in Greece and can attain a length of as much as 6 ft. (1.8 m.). It can climb bushes and trees, from which it is reputed to drop and bite people passing below, thus earning the popular name of *saïta* or *saïtià*—i.e., javelin. This snake is much feared by the peasantry, who, as in most countries, consider all serpents dangerous. Both the above species are, however, quite harmless to human beings, except for the fright caused by their attack or for any rare septic complication that may follow the skin punctures produced by their teeth.

A bite from a poisonless "beast" was surely a cheap enough price to pay for being acclaimed as a god.

I am grateful to Mr. J. C. Battersby, of the British Museum (Natural History), for advice on nomenclature. —I am, etc.,

London, S.W.3. T. STEPHANIDES.

SIR,—In his article "Infertility: Its Incidence and Hope of Cure" (*Journal*, February 22, 1958, p. 429) Mr. H. Campbell explains the failure of Sarai (Genesis XVI and XVII) to bear children to Abraham as caused by her infertility.

In a lecture recently read before our Volunteer Blood Donor Association, Professor F. Rappaport of this hospital explained this failure on the basis of Rh incompatibility. The question which he asked the audience was: Where is the first case of Rh incompatibility described in the Bible? Sarai's blood was homozygous Rh-negative. Her failure to bear live children was due to a high titre of Rh antibodies. Abraham's blood type was heterozygous Rh-positive. With the Angel's blessing a child was conceived, Isaac, who inherited the Rh-negative gene from *both* father and mother. His blood type was homozygous Rh-negative.

We have examined a case very similar to Sarai's one. The woman's blood type was Rh-negative, the titre of Rh antibodies was high, miscarriages many, and a live son was born after the woman received the blessing of the late Holy Rabbi "Hazon-Ish," from Bnai-Brak. There were no Rh antibodies in her last pregnancy, and she gave birth to a male son after many years of real grief.—I am, etc.,

Hadassah Municipal Hospital, Tel-Aviv, Israel. M. RABINOVITZ.

Hogben's "Statistical Theory"

SIR,—In his excellent review of Professor Lancelot Hogben's book in your issue of February 7 (p. 347), Mr. Norman Bailey makes quite plain the author's view that "unless it is possible to rebuild a calculus of judgments on a firmer basis it may well be that the future of statistics in the social sciences is what Anscombe contemptuously calls statistics as the term is used by some continental demographers" ("factual" or "vital" statistics).

The review, however, while implying the general grounds of Hogben's criticisms, does not make quite explicit his main theme, a critical examination and attempted refutation of the views of R. A. Fisher and his school, particularly those expressed in Fisher's book *The Design of Experiments*, a book which has had such an influence on biological research—in Hogben's view an adverse influence. He describes it as "a well-known textbook ostensibly addressed to research workers in general, though in fact almost exclusively concerned with the agricultural field trial," later going on to say, "The juxtaposition of statistical tests employed in comparable circumstances in the milieu of the new pharmacy encouraged the belief that there is a common denominator (the statistical inference) for the objectives which a commercial corporation and a disinterested scientific worker pursue."

Most of us can only view the controversy from the sidelines, but those who think that for the inductive inferences which are the basis of most clinical practice and research the statistical methods now fashionable are at the very least inadequate will welcome Hogben's polemic, and will be grateful to you and your reviewer for bringing the controversy to the notice of the clinician.—I am, etc.,

Liverpool. PERCY MALPAS.

Unilateral Amblyopia

SIR,—I would like to emphasize an important point in Mr. J. Primrose's interesting letter (*Journal*, February 7, p. 363). In the last paragraph of this letter he implies that sight testing under the Supplementary Ophthalmic Service is restricted to six-monthly intervals. In fact, it is limited to one test every twelve months, except in special cases. Cases of amblyopia would certainly need to be seen more frequently than this. They must, therefore, be excluded from this service, which, in any case, is limited to the testing of sight and the supply of glasses. This is not always known to general practitioners and can give rise to inconvenience and delay to patients.—I am, etc.,

Norwich. WILLIAM J. NAUNTON.

Eyes for Corneal Grafting

SIR,—There is a great need for eyes for the purpose of corneal grafting. As a result of a letter in the local paper last week some 20 people immediately offered their eyes after death for this purpose. It has been suggested that such people should wear some sort of badge or disk which would serve two purposes: (*a*) to indicate their wishes in the case of sudden death, and (*b*) to advertise the service, as the wearing of such a badge would provoke comment and produce more volunteers. As far as I am aware there is no such badge in existence, and I suggest that some interested body should produce one.—I am, etc.,

Farnham Hospital, Surrey. F. BEDO HOBBS.

Natural History of the Psychoneuroses

SIR,—The paper on the "Natural History of the Psychoneuroses," by Dr. Harold E. R. Wallace and Miss Marion B. H. White (*Journal*, January 17, p. 144) is of great interest. They have shown evidence that 65.3% of a group of patients considered suitable for psychotherapy recovered spontaneously without it. Their figures, so well in accord with those they quote, might be considered to have "let the cat out of the bag." However, as there remain 34.7% who may not recover spontaneously, it may still be pertinent to inquire what exactly they mean, or indeed any of us mean, by "psychotherapy," whether "formal" or not.

Some invest a good deal of time and money in becoming psychotherapists; while still others give hours of their working week to psychotherapy, though not belonging to any particular school. Their patients return, appointment after appointment, to continue psychotherapy, whether it involves Freudian, Jungian, or eclectic analysis, or simple supportive measures. No matter what verbal formula is used to explain it, the patient appears to believe that he is deriving benefit, and his better adaptation often suggests that he is right.

It was carefully pointed out that no evidence had been produced as to the speed or quality of spontaneous recovery, nor was it stated that psychotherapy was useless. The danger that this last inference may be drawn, particularly by the non-psychiatric reader, is, however, an obvious one. The value of psychotherapy ought certainly to be the subject of controlled scientific inquiry organized on a large scale. It will never emerge from considering the "natural history" of psychoneurosis, nor from mere comparison of one method with another *vis-à-vis* results.

Incidentally, the authors gave no information about the four deaths among the untreated patients. One wonders if they were suicides?—I am, etc.,

Black Notley Hospital, Essex. MICHAEL RAYMOND.

SIR,—The impression by Dr. Harold E. R. Wallace and Miss Marion B. H. Whyte (*Journal*, January 17, p. 144) of the fate of psychoneurosis diagnosed but untreated (formally) is a valuable addition to appraisal of the factors involved. They can hardly be blamed for not attempting to account for all the conditions, although some simple details would have improved the perspective: How selection was made from the waiting-list in the first place, for example. And age; such symptoms are often lifelong in duration, waxing and waning with periodic stresses; they are common in middle and old age.

The difficulties involved in longer-term prediction and prevention are fundamental. They underline the limitations of assessment in terms of individual symptomatology. My experience in a busy neurosis unit is that, when a patient is presented as urgent, more often than not what is happening is that the doctor is becoming involved in the neurosis. By the time this snowball is halted, and the patient extricated, he has much ground to recover.

The authors very rightly point to the importance of relationships at various levels. There is growing evidence that a critical factor in the natural history of the range of mental illness is the attachment and disposal of affect in reciprocity with other people. I cannot think of any more fundamental aspect of personality within our society. Here is where the emphasis of assessment and treatment should be—and as nearly as possible in the sort of situations in which the illness develops, rather than within too artificial therapeutic situations. Perhaps this is why the general practitioner is so successful in the long run.

Nor should we underestimate the value of diagnosis and reassurance. If these are often based on false premises, this is but another condition to elucidate. Many patients know no other way of showing distress than in the doctor's own coin—that is, a physical symptom. Medicine in this sense is as much a part of our humanitarian culture as actual physical illness; and, of course, we are learning that the relation between the two may be close. By this token, in helping a patient with his suffering, according to the best information available at the time, we may be fulfilling our role as physicians.—I am, etc.,

Hornchurch, Essex. H. A. ANDERSON.

Why Suffer from Rheumatism?

SIR,—It was by a curious coincidence that I had just finished writing a letter to the *Medical Journal of Australia* on a somewhat similar topic when I opened the *British Medical Journal* and read with the greatest interest and appreciation the very true letter of Dr. L. A. Nichols, entitled "Why Suffer from Rheumatism?" (*Journal*, November 15, p. 1229). For

many years I have been barking up the identical tree, but apparently no one has paid the slightest attention to the barking. Considering the psychological significance of psychosomatic disturbance, this is really not surprising.

Many practitioners are no doubt familiar with the expressions "nervous tension" and "emotional tension," just as many of the public are familiar with the commoner terms of psycho-analytic literature. This does not for one moment imply that either the professional or layman who uses these phrases has the very remotest idea of the mental mechanisms conditioning them, or of the simplest psychosomatics. This, I am convinced, is due to the fact that very few people fully appreciate just what the "unconscious" is and what it can do. It can no longer be denied that continued emotional stress definitely produces organic tissue changes. However, it does not always follow that, even if they did understand and applied this knowledge to their patients, therapeutically, these patients would respond miraculously. Certainly a large number would benefit, but the application of psychotherapy in depth is a very tedious and painstaking business, and many patients are, in my experience, either too stupid or too emotionally resistant to benefit.—I am, etc.,

Sydney, Australia. E. HASLETT FRAZER.

Carcinomatous Arthropathy

SIR,—Dr. M. Kelly, in his letter (*Journal*, January 31, p. 304) commenting on the memorandum by Dr. E. H. O. Parry entitled "Arthropathy due to Gastric Carcinoma" (*Journal*, October 25, p. 1022), resurrects such factors as "strain," "infection," and "exposure," and implies that they are of importance in the aetiology of rheumatoid disease. I should have thought that they had been decently buried by the report of the Scientific Advisory Committee of the Empire Rheumatism Council.[1] This carefully planned and time-consuming study clearly demonstrated the danger of the acceptance of *uncontrolled* clinical impressions too readily, and most alleged aetiological factors investigated gave negative results.

Nor do I agree that anything is to be gained by abandoning our present concept of rheumatoid disease as a *clinical* entity which differs from other forms of arthritis. Enlargement of concept may be obtained at the expense of definition, and in our present state of ignorance surely clarity of thought is the first essential.—I am, etc.,

Royal Infirmary, Edinburgh. JAMES D. E. KNOX.

REFERENCE

[1] *Brit. med. J.*, 1950, **1**, 799.

Atony of the Female Bladder

SIR,—Many years ago this condition was frequently talked of; to-day it is rarely mentioned as a primary disease, because the bladder neck as an obstructive cause has attracted more and more notice. I think Mr. John Mitchell (*Journal*, February 7, p. 365) calls attention to a good reason for not rushing to the conclusion that this condition is the result of a neurological lesion—namely, the absence of any other sign of neuropathy.

It is now generally recognized that obstruction most commonly originates at the bladder neck in the form of a fibrosis. Data that I published in 1957[1] point to the fact that residual urine in women is often associated with chronic inflammation at the bladder neck. The facts also show that signs of obstruction tend to be more common in direct relationship to the age of the patient. I have never been able to assess endoscopically the degree of obstruction present, that is to say, to estimate the amount of residual urine that should be found.

The practical way of diagnosing a fibrous bladder-neck obstruction is to systematically eliminate other causes of chronic retention. Where the residual urine is considerable, it is my practice to open the bladder and to encircle the bladder neck by an incision made with a high-frequency needle, and to excise the enclosed fibrous tissue. In my hands this technique has been more satisfactory than by the resectoscope method. It certainly gives one the opportunity, before the excision is made, of palpating the internal urinary meatus, which is so commonly found to be stenosed.—I am, etc.,

London, W.1. H. P. WINSBURY-WHITE.

REFERENCE

[1] Winsbury-White, H. P., *Brit. med. J.*, 1957, **2**, 1399.

Preparation for Hysterectomy

SIR,—Dr. Winifred Coppard's letter (*Journal*, January 17, p. 171) is of interest. About four years ago I had occasion to arrange consultation and treatment with a psychiatrist for a highly neurotic woman in the early forties who had had a hysterectomy (but not a vaginal hysterectomy) for fibroids some eighteen years previously and about a year after the birth of her only child. The boy had grown into an aggressive character who liked to go out with friends and to play ice hockey. His mother greatly feared that injury would befall him, but her fears were without justification, though from time to time he did receive small cuts and bruises.

To my knowledge this woman has been to five doctors on account of her neurosis, and has not accepted the prescribed treatment of any beyond the initial stage of that treatment. Upon one occasion I discussed the matter of this woman's married life with her husband, who said to me: "You know, doctor, there is no place."—I am, etc.,

Calgary, Canada. A. ROTHWELL.

Hazards of Meprobamate

SIR,—The warning expressed in your annotation (*Journal*, December 27, p. 1586) that the hazards of meprobamate should also be kept in mind in this country is borne out by several cases which came to our notice in recent months.

Thus a male alcoholic of an inadequate and hysterical personality type had got into the habit of taking large and increasing doses of meprobamate; he turned up at the out-patient clinic in a rather confused state, his speech slightly slurred, asking for "official" medical encouragement to continue taking the drug. He himself felt the tablets were doing him a lot of good, though his wife had become rather alarmed and had persuaded him to come to the clinic.

Another male alcoholic, of an anxious and obsessional personality type, habitually took large numbers of meprobamate tablets, consuming alcohol to excess in the same period and gradually developing a state of confusion and ataxia. Corresponding to the findings reported in your annotation, both these cases were those of alcoholics who in the past had been habituated to other drugs—that is, barbiturates and amphetamines.

However, in another case a non-alcoholic, anxious, obsessional type of woman had gradually increased the number of meprobamate tablets taken at night-time from two (prescribed for her by her doctor) to five. On at least four different nights she took during the night several more of these tablets (maintaining afterwards that at the time she had not been aware of what she was doing), being next morning in an obviously drugged and "intoxicated" state, unable to carry out her work, drowsiness necessitating referral to casualty on one occasion.

In a fourth case a male (inadequate and anxious) neurotic, who was on a regular maintenance dose of one meprobamate tablet thrice daily, took at a time of emotional stress five pints (2.8 l.) of beer a day, an amount which he usually could handle without difficulties. On this occasion, however, he got into a "hazy" state, ascribed by him to the combined effects of alcohol and meprobamate, and, as "I could not remember whether I had taken my tablets or not," he took more meprobamate, gradually reaching a more confused state with vague suicidal ideas.

In general, meprobamate has been found to be of low toxicity, but cases of overdosage—taken with suicidal intent or habitually—have also been observed in several other areas apart from the United States—for example, in Canada,[1] Germany,[2] Scandinavia,[3] and South America.[4] A report on a successfully treated attempted suicide case in South Africa has appeared in your columns.[5] Allergic manifestations after meprobamate intake were noted in Eire.[6]—I am, etc.,

St. Bernard's Hospital, Southall, Middlesex. M. M. GLATT.

REFERENCES

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2 Janz, H. W., *Schr.-Reihe Probl. Suchtgefahr.*, 1958, **4**, 17.
3 Kodahl, T., and Andreassen, J., *Ugeskr. Laeg.*, 1957, **119**, 1067.
4 Brage, D., *Jordan med. J.*, 1957, **15**, 6.
5 Heberden, P., and Cooper, W., *Brit. med. J.*, 1957, **1**, 1513.
6 Barnes, J., *J. Irish med. Ass.*, 1957, **41**, 119.

Foreign Body in the Nose

SIR,—Having read in your issue of January 10 (p. 115) Dr. P. B. Sparke's method of removing a foreign body from a child's nose, may I describe a method which never distresses the child, or the mother, and which I have used for many years without failure?

The instrument I originally used was a hernia director, but any instrument or object of similar thickness, e.g., a blunt knitting needle (metal or plastic) will serve. The child should sit or stand and face directly the operator, who gently passes the instrument horizontally along the inferior meatus as far as it will go. The outer end is then slowly depressed and the object immediately falls out or appears at the nostril, from where it is easily expressed. No doubt the pressure is exerted against the inferior turbinal, which in turn presses the nasal cavity sufficiently to dislodge the foreign body. I have known even a small piece of brown paper to be expelled in this way.

The advantages of this method over removal by forceps, etc., are that there is neither pain nor fear of bleeding.—I am, etc.,

Cwmbran, Monmouthshire. J. FLEMING.

The Art of Consultation

SIR,—In your interesting account of Dr. G. F. Abercrombie's fifth James Mackenzie lecture to the College of General Practitioners (*Journal*, November 29, p. 1349), you quote his illustration of what he regarded as poor and woolly opinion.

"A lady, 14 weeks pregnant, and her 4-year-old daughter, simultaneously developed German measles. The mother knew all there was to be known at that time about pregnancy and German measles, and I immediately obtained confirmation of the diagnosis from a dermatologist. Thence to an obstetrician, who, though clearly in favour of terminating the pregnancy, asked that his opinion be confirmed by a colleague. The second was just as hesitant as the first, and I had finally to take her to a physician before the operation could be done. This physician simply said, 'You can't do anything else.'"

An editorial in the *New England Journal of Medicine*[1] states that no physician is justified in stating categorically that rubella in the first trimester of pregnancy is always associated with a bad prognosis, and a writer in a very recent issue of *Postgraduate Medicine*[2] reached the conclusion that, in summary, it would seem that the risk is not nearly as great as was originally thought and that most authorities now believe that interrupting pregnancy because congenital defects may occur is unjustifiable. Perhaps, after all, Dr. Abercrombie's obstetricians were wiser than he assumed, and the "absolute assurance" of his physician's simple words worth less than he imagined. All in all, it would appear to me that this is a poor illustration of what he was trying to show.—I am, etc.,

London, S.W.3. NOEL H. MOYNIHAN.

REFERENCES

1 *New Engl. J. Med.*, 1952, **247**, 132.
2 *Postgrad. Med.*, 1958, **24**, p. A-18.

An Unusual Extraction

SIR,—I was interested in the letter from Dr. G. G. Noott (*Journal*, January 31, p. 305), having seen a similar case recently. This was also a 9-year-old boy, who, whilst admiring a recently shed deciduous molar, tried it for size in his right ear. One of his schoolfellows happened to pass at that moment, nudged his elbow, and forced the tooth into the depths of the external auditory meatus.

I could not remove the tooth by syringing, but found mosquito forceps admirable for gripping one of the roots.—I am, etc.,

Lechlade, Gloucestershire. D. J. STEPHENS.

Aspirin Plain and Buffered

SIR,—Mr. J. H. Chapman (*Journal*, February 14, p. 442) claims that the aspirin in "solprin" brand of soluble aspirin, under controlled experimental conditions, passes into true solution, but he does not specify the conditions.

On inquiry, I was informed by his firm that one tablet "in carefully controlled conditions" will dissolve in 100 ml. of water at 20° C. (68° F.). As each solprin contains 5 gr. (0.324 g.) of aspirin, it follows that a similar claim could be made for any 5-gr. aspirin tablet, plain or buffered, because it lies within the range of solubility (1–300) of aspirin itself.

As few patients will find it convenient to take an aspirin tablet in carefully controlled conditions, I agree that the fine suspension on disintegration, advocated in your leading article, is the most desirable quality to be looked for in the everyday use of aspirin tablets. I also agree that solprin possess this quality, in common with other "soluble" aspirin tablets and with some formulations of plain aspirin tablets.—I am, etc.,

Oxford. W. TRILLWOOD.

Obituary

F. W. J. A. LAMB, M.D., D.P.H.

Dr. F. W. J. A. Lamb, formerly reader in human physiology in the University of Manchester, died on January 11 at Clara, in Ireland. He was 84 years of age.

Francis William John Alexander Lamb was born in Dublin on June 8, 1874, the son of William Lamb, LL.D. He graduated in medicine in 1901, after studying in that most colourful of medical schools of the 'nineties, Trinity College, Dublin. His fellow-student and personal friend, Oliver St. John Gogarty, has immortalized those days in *Tumbling in the Hay*, and in its pages the student Lamb may be recognized. Nor was medicine his only interest—the classics had already claimed him, and his devotion to them was kept up, as witnessed by the occasional Greek text nestling among the physiological books under his arm.

After a short period in general practice he turned to physiology, holding first a junior appointment in Cardiff. There he had to teach biochemistry as well as histology and practical physiology, and there also he laid the foundation of his contribution to medical education by establishing clearly in his mind the importance of the practical approach in the teaching of physiology. He came to Manchester as senior demonstrator in 1909, and was later made lecturer. The war years were spent in Ireland as assistant professor at Trinity College, while Sir Henry Thompson was at the Ministry of Food. In 1919 he returned to Manchester as lecturer in physiology and took charge of the department, for the chair of physiology was at that time vacant. In those difficult days of large post-war classes he devoted himself heart and soul to his teaching.

It was after the appointment of A. V. Hill as professor in 1920 that Lamb began to make use of his experience and to devise his course in human experimental physiology, thereby making a unique and far-reaching contribution to the study of physiology. The course, ever being modified as time went on, formed the basis of many similar courses in Europe and in America. The scientific investigation of the carriage of the gases by the blood was being pursued by J. S. Haldane in a way which captured the imagination of the physiological world. But it took real courage to introduce air and blood-gas analysis apparatus to plain medical students, and Lamb did so with conspicuous success. To him and to him alone belongs the credit of presenting physiology to medical students as something personal and vital and affecting the whole of their future practice: he laid the stress on the first word of human physiology. The contribution which he has made to medical education was a great one, as can be found in his book *An Introduction to Human Experimental Physiology*, published in 1930. In the previous year he had served as vice-president of the Section of Physiology and Biochemistry at the Annual Meeting of the B.M.A. in Manchester. When he retired in 1939 it was said that he would be missed most by his demonstrators and research workers. Not only had he taught them much but he had gently restrained their enthusiasms in thrusting newly acquired, ill-digested, and often useless knowledge on the unfortunate medical student, and he constantly reminded them of the task in hand—the making of useful medical men and women.

He was a frequent visitor to Southern Ireland, where he had many friends and where he went to live in his retirement. His father, a clergyman of the Church of England, had been a keen collector of books, and Lamb inherited the same interest. He was a most valued member of the University Medical Library Committee, for he had a remarkable knowledge of old books in general and old medical books in particular, and was such a friendly, scholarly man.

H. M. D. SHEPHERD, M.D., F.R.C.P.Ed.

Dr. H. M. D. Shepherd, consultant physician to the Dudley Road Hospital, Birmingham, died suddenly at Exeter on January 18. He was 51 years of age.

Hugh Michael Denne Shepherd was born at Dundee on December 8, 1907, and was educated at Glenalmond and at Edinburgh University, where he graduated M.B., Ch.B. in 1932. He proceeded to the M.D., with commendation, in 1937 and in the same year was elected a Member of the Royal College of Physicians of Edinburgh, becoming a Fellow of the College in 1947. After graduation he held the post of house-surgeon at the Edinburgh Royal Infirmary before taking other resident appointments at Leicester, Worcester, and Redhill Hospital, Edgware, where he was resident medical officer. He then joined a partnership in Shanklin, and was appointed to the staff of the Royal Isle of Wight County Hospital as honorary assistant physician. During the second world war he served in the R.A.M.C., and as a lieutenant-colonel was in charge of a hospital in the Middle East. He was mentioned in dispatches in 1945. A paper he wrote on the effects of heat in Iraq was published in the *Journal of the R.A.M.C.* On his return to civilian life he decided to specialize in medicine, and he joined the staff of Dudley Road Hospital, Birmingham, as a consultant physician in 1946, remaining there until his untimely death. He leaves a widow and two sons.

J. W. T. writes: The sudden and unexpected death of Hugh Shepherd at the early age of 51 has come as the greatest shock, and has brought much distress to his numerous friends both inside and outside the medical profession. It seems quite impossible for us, his colleagues, to believe that we shall never again see that dearly familiar and much respected figure moving among us in our daily life at the hospital. Hugh was perhaps difficult at first to get to know, as he was essentially shy, reserved, and conservative in his outlook, but once the barriers were down and his assessment made the most true and loyal friendship blazened forth and was permanently yours. He was conscientious and zealous in the extreme in all matters that he undertook.

His professional standards were set so high that twenty-four hours in the day would not suffice. For him his patients' care was a sacred and dedicated trust. In consultation Hugh's opinion and diagnosis were uncannily accurate, being the result always of much considered thought and work. One never discussed a case with him without coming away a wiser, and somehow humbler, man. We admired Hugh for his great modesty and lack of all human conceit and ostentatiousness. He lived according to those ideals and traditional loyalties which now tend to be so sadly disparaged. Above all perhaps he hated humbug and every form of falseness. A very able committeeman himself, he often could elucidate the most intricate and complicated discussion by one straight shaft of common sense so simple and yet so pertinent that all would seem ridiculously clear. Knowledgeable about so many facets of life, he was the ideal companion. I shall always remember and treasure those days that Hugh and I spent so energetically in the spring sunshine enticing with our flies the early trout. Our sympathy goes out to his widow in her tragic loss, but at least she will be able to hold out to her two young sons the example of Hugh Shepherd's abounding goodness and high ideals.

A. E. PREISS, M.D., D.M.R.E.

Dr. A. E. Preiss, consultant radiologist to King Edward Memorial Hospital, Ealing, died at Colindale Hospital on January 29 from coronary occlusion. He was 59 years of age.

Born in Moravia, in Velka, on August 6, 1899, Arnost Ernest Preiss served in the Austrian Army in the first world war, at first in Russia and, later, on the Italian front. After the war he studied medicine and graduated M.D. from Brno

University in 1925. He developed a special interest in radiology, working for a time in Vienna under Holzknecht. Later he returned to Czechoslovakia, where he practised in Opava. In 1939, when his country was occupied by the Germans, he escaped, and joined the Free Czech forces as a medical officer, serving in France and narrowly escaping capture in 1940. He reached England with the Free Czech forces, and while in this country obtained the D.M.R.E. at Cambridge in 1942. He was radiologist to the Czech Military Hospital at Hammersmith. In June, 1944, he went as a volunteer with the British Army into Normandy, and continued with it to Brussels, where he joined the Czech forces besieging Dunkirk. After the war he returned to Prague and was there when the Communists seized power. He soon saw the need to move, and, leaving all his possessions, managed to return to England. After a short period in Swindon he was appointed, in 1950, consultant radiologist to the King Edward Memorial Hospital, Ealing, and the Queen Victoria Hospital, Hanwell. At this point in his career another blow of fate confined him to hospital for a year, but he recovered and continued in these appointments until his death. A bachelor, he was rather reserved, but his friends found in him a cosmopolitan culture and a wide interest in the arts, and he was himself an amateur artist. Helpful and level-headed, he gave of his best in radiology, never sparing himself, and his work was valued by his colleagues. Life had been difficult for him, but he remained undefeated by the blows of fate. He will be remembered with affection and esteem.—E. J. E. T.

LÉON GÉRIN-LAJOIE, M.D., D.Sc., F.R.C.S.(C.) F.A.C.S.

Dr. L. Gérin-Lajoie, professor of gynaecology at the University of Montreal and president-elect of the World Medical Association, died on February 14 in Notre Dame Hospital, Montreal. He was 63 years of age.

Léon Gérin-Lajoie was born on March 14, 1895, in Montreal. A medical student at the University of Montreal, he graduated in medicine in 1918 and immediately joined the Royal Canadian Army Medical Corps for service in the first world war. After demobilization he worked as a postgraduate in Paris until 1922, when he returned to Montreal and was appointed junior assistant in the gynaecological clinic of Notre Dame Hospital. In 1937 he became director of the clinic, and two years later he was appointed professor of gynaecology at the University of Montreal. He was also vice-dean of the faculty of medicine for several years and a trustee of the Banting Institute. A fellow of the Royal College of Surgeons of Canada and of the American College of Surgeons, he had held the office of president of the Société Médicale de Montréal and of the Société de Chirurgie de Montréal in consecutive years. In 1956 the University of Laval conferred on him the honorary degree of D.Sc.

For many years Dr. Gérin-Lajoie had been active in the affairs of the Canadian Medical Association, and he succeeded Dr. T. C. Routley as president of the Association in 1956. A sincere advocate of international collaboration in medicine, he was president of the International Federation of Obstetricians and Gynaecologists, and he was to have been installed as president of the World Medical Association in Montreal next September.

Dr. Gérin-Lajoie had been associated with the work of the W.M.A. from its inception. A French Canadian, he soon found himself in demand as an unofficial interpreter at W.M.A. functions and council meetings. He seemed to get a special enjoyment out of translating after-dinner speeches, and not uncommonly his French version of a speech originally made in English was a far more polished effort, with deft touches introduced by the interpreter. And so in time Gérin-Lajoie became official interpreter at the council meetings of the W.M.A. and at many of its committee meetings; this he combined with the position of assistant to the chairman of council. Whenever W.M.A. visits were held in Europe, Gérin-Lajoie and his charming and ever-youthful wife always ended up in Paris, the one city that for them represented their racial and spiritual heritage. These two friendly people were great ambassadors for their own country in the medical circles of the various countries the W.M.A. visited. Gérin-Lajoie will be sorely missed by a great host of friends who will wish to extend their deepest sympathy to his widow.

H. S. ATKINSON, M.B.E., B.M., B.Ch.

J. R. E. writes to supplement the account of Dr. H. S. Atkinson's career printed in the *Journal* of February 21 (p. 515), and to offer a personal appreciation.

Henry Atkinson went from Merchant Taylors' School to St. John's College, Oxford, where he was a Sir Thomas White science scholar. At the London Hospital, where he held numerous appointments after graduation, he won the Anderson prize for clinical medicine.

In 1934 he went to Redhill to join a long-established practice, and soon afterwards was elected physician to the East Surrey Hospital. He continued to serve this hospital until his death, being also a member of its house committee and a member of the Redhill group advisory committee. Both as physician and practitioner he was outstanding, bringing to both the benefits of long postgraduate training, great personal ability, and a remarkable capacity for hard work in the service of others. He set himself high standards, and very quickly became both respected and beloved, a source of great though quiet strength to very many people in a large area.

A fundamental feature of Henry Atkinson was his ability to combine scrupulous attention to detail in everything, especially in the care of patients, with an acute awareness of the wider responsibilities of the doctor to his community. Having joined the Royal Air Force Volunteer Reserve in 1939, he served throughout the second world war, most of the time as a medical specialist in North Africa and Italy, with the rank of wing commander. He returned in the latter part of 1945 to all his pre-war clinical activities at Redhill, but added to them the care of the general medical and post-operative surgical patients in three London Hospital annexes. Despite this very large weight of clinical work he still set out to fulfil his responsibilities to the profession and to the community as a whole. He became vice-chairman of the Reigate Division of the British Medical Association, and was honorary secretary and at one time vice-president of the Surrey Benevolent Medical Society. He gave his whole-hearted support to the East Surrey mobile physiotherapy unit, which had been formed in 1943, and gave it invaluable service for many years as chairman of its committee. He was also, from its foundation, an active supporter of the borough of Reigate Council of Social Service.

Henry Atkinson's death, at so young an age, is a grievous loss to the patients, the hospitals, and the community which he served so well. He was an exceptionally good doctor. The combination of a large general practice and his work as physician to the East Surrey Hospital and at the Banstead, Fairfield, and Croft annexes of the London Hospital gave him unusual clinical experience. His intrinsic interest in medicine and in his patients kept his knowledge accurate and wide, and he had a clear, incisive, but adaptable mind. Fine clinical judgment and competence were therefore almost inevitably his. There was, however, much more to him than that. He was a man of complete integrity and with very high standards, taking responsibility with ease but never lightly, and progressive while retaining a deep and firm attachment to the best traditions of his profession. Patients and colleagues unhesitatingly trusted and respected him.

Outwardly he was a quiet and entirely unostentatious person. A most natural courtesy and an ever-present sense of humour made him as delightful a companion as his discriminating and thoughtful attitude to life and his wide interests made him both interesting and stimulating. He was a leader, and led by example; for he was essentially a

man of action. When he decided that something should be done, he would quietly and efficiently proceed to do it. Thus he would drive a patient to hospital in his own car, or with gentle firmness assist the convalescent's first steps to rehabilitation. In the same manner his awareness of the doctor's wider responsibilities led him to action on behalf of the mobile physiotherapy unit and the Air Training Corps.

Yet despite his very many activities and duties he appeared always entirely unhurried and unruffled. No single patient—in hospital, consulting-room, or home—could ever have felt other than that Henry Atkinson had all the time in the world just to help him as a doctor and as a friend. He was able to give this impression only because he was most efficient in all aspects of his work, and orderly, almost meticulous, in the management of his own time. For this reason also he was able to make and enjoy a full and most happy family life. To his widow, his two sons, and two daughters we offer our deepest sympathy. Henry Atkinson was a fine and happy man, and one who was an example of what a doctor should be.

W. W. writes: When we heard of the sudden death of Dr. H. S. Atkinson most of us felt, I think, that it was impossible. We were stunned by a sense of total loss. I am sure I am writing in the name of a multitude, including late partners, partners, colleagues, friends, acquaintances, patients, and all who had had the good fortune to be associated with him in any way. Later, very gradually, we awoke to realize that it was not a total loss we had suffered. His memory at least can never be taken from us. His capabilities, appointments, and achievements in the medical world I leave others to assess and relate, but I know we should all like to think of the personal characteristics that made up a most lovable man, who might well be envied and emulated by us who are left. There was something eminently steadfast and dependable about Henry Atkinson, something upright and reliable, something cheerful and kindly, that made knowing him a pleasant thing in life. Total loss, therefore, we have not suffered. We have the memory still of a very loyal English gentleman, an unusually able medical man, and a sure help to those in trouble. Let us therefore keep it fresh, salute his widow and children with deepest sympathy, and profit from the privilege of having known him.

Medico-Legal

ANAESTHETIST GUILTY OF MANSLAUGHTER

Drug Addiction Admitted

Dr. W. P. S. Gray, aged 36, was at the Old Bailey on February 20 sentenced to 12 months' imprisonment for the manslaughter of a 2-year-old boy, who died after an operation at Chase Farm Hospital, Enfield, at which Dr. Gray was anaesthetist.

Dr. Gray pleaded guilty, and Mr. Christmas Humphreys (prosecuting) said that Dr. Gray had admitted being an addict to the inhaling of anaesthetics for seven years. The boy, Keith Goold, died a month after the operation, from softening of the brain due to anoxia during the operation.

An account of the prosecution's case, as presented at the preliminary hearing before the Tottenham Magistrates Court last month, is given in the issues of the *Journal* for January 31 (p. 308) and February 7 (p. 376).

Plea in Mitigation

Mr. Gerald Gardiner, Q.C. (defending), said that Dr. Gray expressed deep remorse and sympathy for the boy's family. He had always accepted responsibility for what had happened. He had devoted the whole of his life to the relief of suffering in the field of anaesthetics, and had done a great deal of research work in anaesthetics and on the development of apparatus. He had now resigned from all his appointments, and he did not intend, even if he could, to work again in the field of anaesthetics. It would obviously be a matter for the consideration of the General Medical Council whether he should be permitted to practise as a doctor in the future. His work was now ruined.

"If the doctors who knew of his addiction had taken action previously, the tragedy of the boy and Dr. Gray would have been avoided," said Mr. Gardiner.

Mr. Justice Donovan, passing sentence, said: "I do not want to make any comment on your weakness, except to say that you indulged in it at a time when another human life was in your hands."

He took into account Dr. Gray's excellent record and character, and his frankness. "Your punishment will not end here," the Judge continued. "In those circumstances I do not think it is necessary to inflict a severe sentence, which this crime of manslaughter usually attracts."

Dr. Gray's Addiction Well Known

Mr. Humphreys said that the anaesthetic was given through a Boyle's machine, which was in perfect working order. The anaesthetic contained a mixture of nitrous oxide and a comparatively new anaesthetic, "fluothane" (halothane), together with oxygen. Nitrous oxide could be used as a drug, and was known to be so used sometimes by people working in hospitals. The effect was to give a feeling of well-being and clarity of mind. It was easy to become habituated, and Dr. Gray had admitted that he had been an addict for seven years.

A surgeon at the operation in question had said that in 1957 he knew of Dr. Gray's addiction and talked about it, continued counsel. Another anaesthetist said he too knew about it in 1958. "Indeed, putting together the evidence of persons then at the hospital, it would seem that the addiction and practice of Dr. Gray was perfectly well known."

Mr. W. D. Coltart, surgeon at the hospital, called for the defence, said he had known Dr. Gray since 1948 when he was senior resident anaesthetist at Bart's. In 1950 he had been made senior registrar in anaesthetics there, an appointment usually given to those showing particular promise. Mr. Coltart said he had operated at Chase Farm with Dr. Gray as the anaesthetist. "I thought he was excellent and I had the utmost confidence in him." Dr. Gray had contributed original research in anaesthetics. "His real interest in life was anaesthetics, and he appeared to have a vocation for it."

Answering Mr. Justice Donovan, Mr. Coltart said it was very difficult to generalize on what a hospital would do in a case such as Dr. Gray's.

"Is this Unprecedented?"

The Judge: "May I take it this is an unprecedented thing, or is it something to which people are prone?"

Mr. Coltart replied: "It does happen. But I have never heard of this sort of tragedy occurring." He had never heard before of an anaesthetist indulging in halothane. He would have thought that an anaesthetist would never become incapacitated in that way. He would either become unconscious or drop to the floor. It seemed to him there must be something different about halothane. It appeared to produce euphoria. Perhaps if Dr. Gray's colleagues had realized the extra dangers of halothane they might have taken more vigorous action.

"Had I known of this indulgence by Dr. Gray I would have insisted he gave up anaesthetics for a time and had treatment; and, if he had refused, I think I would have reported him."

Ministry Statement

A spokesman of the Ministry of Health said after the case: "The Minister of Health will of course consider the implications of this case, but he cannot do so until he is fully acquainted with all the facts that have come out in court."

ANOTHER RATING APPEAL

SOCIETY OF MEDICAL OFFICERS OF HEALTH

[FROM OUR LEGAL CORRESPONDENT]

Earlier this month we reported the General Nursing Council's unsuccessful appeal to the House of Lords about the rating of its premises (*Brit. med. J.*, February 7, p. 375). Now the Society of Medical Officers of Health is having rating trouble. On February 9 the Court of Appeal ruled against the Society, though leave was granted to appeal to the House of Lords (*The Times*, February 10).

Scientific Societies Act

In a rating case in 1951 the local valuation court for North-east London held that the Society of Medical Officers of Health was exempt from rating in respect of its premises at Tavistock House under Section 1 of the Scientific Societies Act, 1843, on the ground that the Society was instituted for the purposes of science, literature, or the fine arts exclusively. A new valuation list came into force on April 1, 1956, and the Society's property was entered in the list with a figure for rateable value. Not unnaturally the Society claimed that, as all the relevant circumstances of its constitution and activities and the uses of its premises were unchanged since the 1951 decision, it was still entitled to exemption. The local valuation court agreed with the Society, but the Lands Tribunal decided that the matter was not concluded by the 1951 decision. The Society then appealed to the Court of Appeal, which upheld the decision of the Lands Tribunal by a majority of 2 to 1, but gave leave to appeal to the House of Lords.

Court's Decision Not Final

The majority view was that, since the jurisdiction of the local valuation court was limited to deciding something in relation to the then existing list, its decision could not amount to *res judicata* on a question relating to a new list.

Lord Justice Sellers, dissenting, said that the question to be decided was the same for both lists—namely, the Society's right to exemption under the Act of 1843. Under present legislation there was a prospect of a new list every five years; and if, as it seemed, it could take the best part of five years to litigate this question to the House of Lords, then unless the decision regarding one list applied to the next list the whole process could at once be started again. There could be two conflicting decisions of the same court on litigation between the same parties on the same subject, the only difference being an interval of five years. Lord Justice Sellers said that, unless restrained by authority, he would reject the view that there could be no finality on any rating issue.

Medical Notes in Parliament

REBUILDING ROYAL FREE HOSPITAL

Mr. RICHARD THOMPSON, Parliamentary Secretary, Ministry of Health, answered a complaint made by Mr. M. CLIFFE (Shoreditch and Finsbury, Lab.) on February 20 about the projected closure of the Royal Free Hospital and Medical School, on which he said there was a great deal of anxiety in the locality.

The decision to rebuild the Royal Free at Hampstead, Mr. THOMPSON said, was founded on the recommendations of the Goodenough Committee and the London Hospital survey in 1944 and 1945. It was recommended that certain teaching hospitals should emigrate from central London in view of the likely decline in population and what was considered to be an over-concentration of medical schools in the London area. After the setting up of the Health Service in 1948 a group of hospitals were designated as a teaching group, with the long-term aim of rebuilding the Royal Free at Hampstead. A joint proposal was agreed in principle by the boards of governors, the N.W. Metropolitan Regional Board, and the University Grants Committee. When the new hospital had been built the intention ultimately was to close the Royal Free Hospital, the London Fever Hospital, the Elizabeth Garrett Anderson Hospital, and the New End Hospital at Hampstead.

It was the latter part of the scheme that had aroused controversy. The London Local Medical Committee had welcomed the rebuilding at Hampstead, but would prefer the retention of the Royal Free, the Elizabeth Garrett Anderson, and the London Fever. They were inclined at present to want both things—the new hospital at Hampstead, and the continuing use of the existing buildings. Representatives of the general practitioners and the London Medical Committee discussed last November the problems arising in central London bearing on the proposed removal of the Charing Cross and Royal Free Hospitals. It was agreed that they would need a great deal of further study, and everyone realized that, as the proposed closure was several years distant, discussion should be deferred until the further needs of the area took shape and were apparent. The Royal Free, as a teaching hospital, served a much wider area than Finsbury. It was necessary also to think of such factors as population trends and the development of Health Service hospitals on the periphery of London. In a few years this might show a very different pattern of hospital need.

If all went well a start might be made on the Royal Free in 1960–1. It would take several years to complete. Building would have to go on while the hospital on the site was continuing to give full service; it would not be quick or easy.

MENTAL HEALTH BILL IN COMMITTEE

The detailed scrutiny in committee of the Mental Health Bill began on February 10, and in their first four meetings the 45 M.P.s had almost completed Parts I and II. These initial discussions covered the definition of psychopathic disorder and the provision by local health authorities of community care services, on both of which the decision was taken to a vote.

Visits by Ministry Experts

Part I repeals the Lunacy and Mental Treatment Acts, 1890–1930, and the Mental Deficiency Acts, 1913–38, dissolves the Board of Control, and establishes mental health review tribunals.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) sought by an amendment to Clause 2 to ensure that the duties of inspection or rights of reporting previously vested in the Board should be transferred to the Minister. This gave Mr. D. WALKER-SMITH the opportunity to assure her and others that there would be a system of visiting by experts from the centre to see that all was well in the hospitals, to convey new ideas as they went round, and to act as a clearing house and a channel for the dissemination of ideas throughout the service. No statutory provision for this was needed in the Bill, because the Minister could and should do it as part of his responsibility for the Health Service as a whole. Various types of people would do this as part of their general duties in the Ministry of Health—medical officers, nursing officers, dietitians, and other experts, and general administrators. He was anxious that this process—he applied to it the phrase "cross-fertilization of ideas"—should be thought of *not* in the phraseology of inspection and reporting, but in the concept of visits, recommendations, and discussions of the results with managers and management committees. He would do his best in the annual reports of the Ministry to contribute to the collation of ideas and the spread of information. This was accepted, and the amendment withdrawn.

Psychopaths

Clause 4 contains the definition and classification of mental disorder. Dr. DONALD JOHNSON (Carlisle, Con.) wished

to exclude the definition of psychopathic disorder in subsection (4), and in so doing voiced the dismay that had been expressed to him by persons in charge of mental hospitals at the prospect of having psychopaths thrust on them and of having to deal with them in the therapeutic atmosphere most hospitals were seeking to establish. He quoted the views stated by Dr. L. Neustatter (in a letter to *The Times* on February 3); spoke of the serious doubts whether the psychopath, as defined, was susceptible to medical treatment; and was apprehensive that the general terms used in describing behaviour might automatically render psychopaths liable to detention just on a doctor's certificate, apart from any court procedure.

Mr. KENNETH ROBINSON (St. Pancras North, Lab.) accepted that these were difficult people, not welcomed by any medical superintendent or any hospital, but thought the answer was to create for them special units, at least one in each region. He thought much of the difficulty that had been voiced about treatment was probably because the psychiatrists were talking about medical treatment in the clinical sense. Taking treatment in the wider sense, including what he would call social treatment, there was something, and possibly a lot, that could be done for this difficult and unfortunate category.

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) admitted from his own experience the disruptive effect of a psychopath in a ward, and endorsed the idea of special units. "Medical treatment" in the sense of treatment by drugs, operations, and so forth, there was not, but some psychiatric treatment was available—one example was group therapy in teaching self-discipline.

Safeguards Thought Adequate

The MINISTER argued, in reply, that the approach in the Bill, although no one would claim that it was the end of the road, was the most promising approach that had so far been revealed. Looking ahead to Clause 142 (the interpretation clause) he pointed out that medical treatment included nursing, and care and training under medical supervision. The effect of the amendment would be to exclude psychopaths from the scope of the Bill, and therefore from both voluntary treatment and compulsory treatment. It was important not to "write off" the possibilities of voluntary treatment. On the compulsory procedures, he emphasized that to establish psychopathic disorder there must be a medical diagnosis covering each and every one of the requirements of subsection (4). The Royal Commission had said that the difficulty flowed not so much from diagnosis as from the language—finding terms in which the condition could be described in everyday language.

He entirely accepted that there should be appropriate safeguards, and those contained in the definition (as distinct from procedural safeguards to be considered later) were these. First, the disorder must be persistent. Second, it must be manifested in recognizable results—aggressive or irresponsible. Third, it must require or be susceptible to medical treatment. In some cases it might be for the tribunal to decide whether these definitions were satisfied. The second category of safeguards for the liberty of the subject were contained in Clause 26, relating to compulsory admission. On the question of segregation, the Minister said that discussions had been in progress with regional hospital boards on the rearrangement of accommodation according to the new classifications. The discussions went wider than the psychopath aspect, and arose broadly in all the categories now classified as mental defectives. They might well involve this special arrangement for psychopaths, but where it was appropriate it could often be achieved within a hospital, without necessarily building a separate unit.

"Seriously Irresponsible" Not Too Broad

This amendment was withdrawn, but on a later one, moved by Mr. K. ROBINSON to make the definition in subsection (4) read "dangerously irresponsible conduct," instead of the "seriously irresponsible" used in the Bill, the committee had its first division. His objection was that "seriously irresponsible" was very broad and could lead to an extremely wide variation of interpretation. Dr. JOHNSON supported him. Dr. BROUGHTON thought the amendment would leave out some persons suffering from psychopathic disorder who should be included. Mr. SOMERVILLE HASTINGS (Barking, Lab.) said it would be wrong to wait until behaviour was dangerously abnormal.

Mr. WALKER-SMITH drew attention to the dual manifestation of mental disorder in the subsection: it must be either abnormally aggressive conduct or seriously irresponsible conduct. In either case there must be medical diagnoses of a persistent state of disorder, and it must be susceptible to medical treatment. The amendment would limit the application to physical danger to others or to themselves. That would rule out a good many inadequate psychopaths. There was a material consideration, in that, although the seriously irresponsible type of psychopath could be admitted compulsorily under Clause 25 for observation at any age, he could be admitted compulsorily for treatment under Clause 26 only if he was under 21, unless he was a court case. The effect of the amendment on court cases would be serious and retrogressive. There would be no power of compulsory detention to enable the courts to make a hospital order, or to enable the Home Secretary to make a transfer direction from prison. The courts would be forced back to imposing prison sentences or probation with conditional psychiatric treatment. The amendment was rejected by 24 votes to 4.

Directions to Local Authorities

The other division took place on the provisions relating to the functions of local authorities. Dr. EDITH SUMMERSKILL wanted to strengthen Clause 6 by inserting in it an additional subsection putting on health authorities the duty of submitting to the Minister, within two years of the passing of the Bill, plans for carrying out the mental health services for which they are to become responsible. She urged that if the Bill was to be effective local authorities must take it seriously immediately. It was essential to set a date for the culmination of the preparatory work involved, including the necessary consultations with the regional boards, boards of governors, and executive councils to secure an integrated service. Unless some stimulus was applied there would inevitably be authorities and individuals who would pay lip service to the importance of the Bill but refrain from taking positive action.

Mr. K. ROBINSON said the most disappointing feature of the Bill had been the discovery that the powers of local authorities to provide for community care remained—contrary to the report of the Royal Commission—partly permissive, and not mandatory. Local authorities would have no inducement to look for buildings or staff unless they had some target to aim at.

Mr. WALKER-SMITH, yielding to none in his desire for the steady progress and gathering momentum of local authority services, saw the issue not as one of principle but as the best way of achieving an object that all desired. It was necessary that Clause 6 procedures should be within the pattern of Section 28 of the National Health Service Act, 1946. This was governed by the provisions of Section 20, requiring that proposals should be submitted within such period as the Minister might specify. In his view it would be best to leave the Bill as it stood, and proceed by direction.

He had in mind the issue of two directions, almost immediately after the Bill was passed. The first would require health authorities to make arrangements for the care and aftercare of the mentally disordered within the scope of section 28(1); and the second would direct that proposals should be submitted within a stated period, say six months. The advantage of this method would be that it would give greater flexibility. The proposals submitted by local authorities in response to the second direction would give a programme of development of individual services. Some, such as training centres, would be in confirmation of an existing duty and would be capable of

immediate operation. Others, such as adequate provision of residential accommodation, would be spread necessarily over a longer period. It might provide for the submission of phased programmes for residential accommodation within, say, eight months.

This did not satisfy Dr. SUMMERSKILL, or Dr. BROUGHTON and other Opposition members, although the Minister subsequently pointed out that once the directions were in force the obligation was no longer permissive but became mandatory. Dr. SUMMERSKILL paraphrased the Royal Commission's recommendations in the phrase "Use your powers now," and insisted that only by statutory authority could pressure be brought on local authorities. Her amendment was ultimately rejected by 19 votes to 13.

QUESTIONS IN THE COMMONS

Effect of Noise on Health

Mr. H. MARQUAND (Middlesbrough, East, Lab.) asked the Minister of Health on February 18 what studies of the effect of noise upon the health of industrial workers had been or were being undertaken by the Medical Research Council. Mr. WALKER-SMITH stated that the Medical Research Council had during the past 30 years sponsored studies of the effect of noise in industry; these had been concerned both with the general psychological effects which might be produced and with the more specific effects upon the sense of hearing. At the present time surveys were being undertaken to define the normal deterioration of hearing which occurred with age and the extent to which this might be modified by exposure to industrial noise.

Cremation Certificates

Mr. J. REEVES (Greenwich, Lab.) asked the Home Secretary whether he was aware that doctors were still charging more than was recommended by the British Medical Association for the signing of cremation certificates B and C, and that he had in his possession a receipt of two doctors charging £8 8s. for certificates B and C for one cremation of one whose relatives could ill afford such a sum; if he was aware that such excessive charges were detrimental to this hygienic method of disposing of the dead, and were becoming a public scandal, and what steps he was taking to check this tendency. Mr. D. RENTON, Under Secretary, Home Office, replied that the Home Office had recently embarked upon a review of the Cremation Regulations, and this matter would be included in the review.

Mr. REEVES said that all the efforts that had been made towards a voluntary agreement had been unsuccessful, and time after time these voluntary arrangements had been violated. He hoped the working party would take seriously into consideration the information that was available. Mr. RENTON said that they would no doubt bear in mind what Mr. Reeves had said.

Manufacture of Drugs

Mr. M. EDELMAN (Coventry, North, Lab.) asked the Minister of Health on February 16 if he would make inquiries, in the course of his regular investigations into manufacturing costs where monopoly patents applied, as to the charge made by an American company's subsidiary operating in the United Kingdom of 40s. per 100 ten-milligramme tablets of mecamylamine hydrochloride, a drug on current supply to the Health Service, in view of the fact that this material was available in Europe at £100 per kilo and that the profit on the price to the Health Service, after allowances for manufacturing costs, was approximately 990%. Mr. WALKER-SMITH replied that he understood that this drug was classified by the Standing Joint Committee on the Classification of Proprietary Preparations as a new drug of proved value not yet standard, and its price was therefore not regulated at present by the scheme agreed with the pharmaceutical industry. He did not know how Mr. Edelman had made his calculation, but if he would give him details he would make some inquiries of the manufacturers.

Vital Statistics

Influenza and Pneumonia

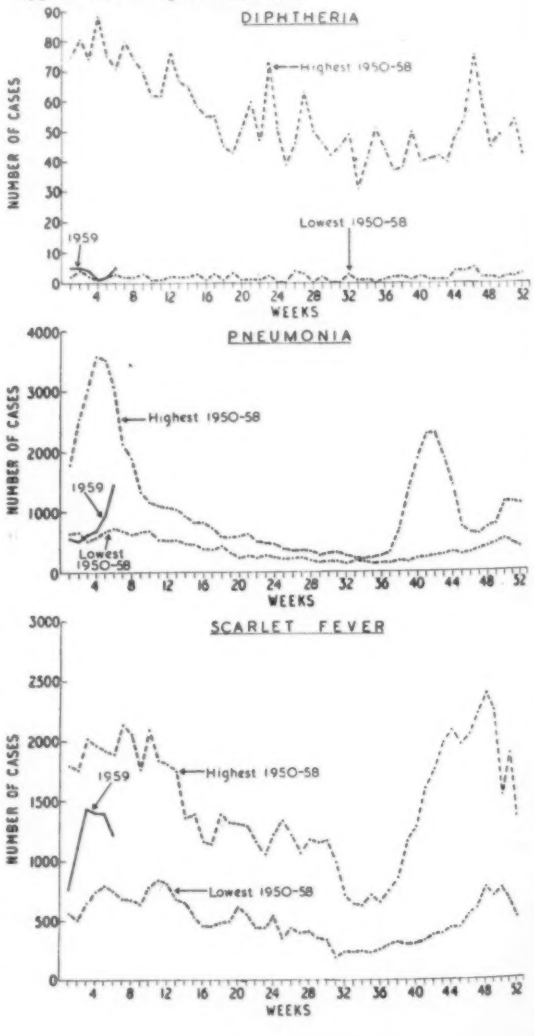
The number of deaths from influenza in England and Wales again rose sharply in the week ending February 14, when 455 were reported, compared with 144 in the previous week. Deaths from pneumonia numbered 1,373. The number of cases of pneumonia notified was 1,465.

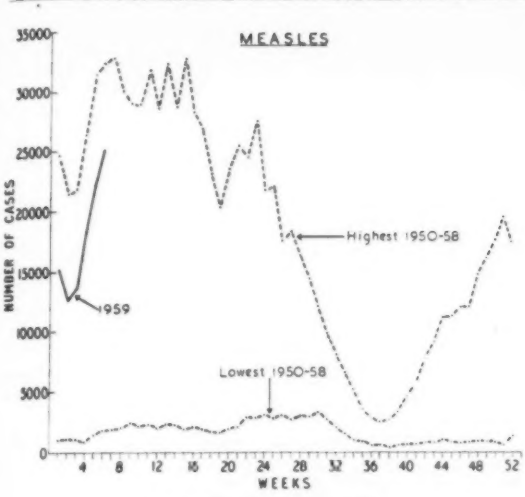
The age distribution of the influenza deaths was as follows: under 15 years, 11; 15–64 years, 142; 65 and over, 302. In Birmingham 55 deaths from influenza were recorded, and in London 44. The most severely affected areas are the North-west, the Midlands, and London. In some outbreaks virus A (Asian) has been identified, in others virus B.

In the great towns of Scotland 29 deaths from influenza were recorded, in Northern Ireland 1, and in Eire none.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ————. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





Week Ending February 14

The largest fluctuations in infectious diseases in England and Wales during the week ending February 14 were increases of 2,987 for measles, from 22,170 to 25,157, 522 for acute pneumonia, from 943 to 1,465, 52 for dysentery, from 1,294 to 1,346, and 30 for whooping-cough, from 758 to 788; the only large decrease was 171 for scarlet fever, from 1,389 to 1,218.

The largest increases in the incidence of measles were 642 in Yorkshire West Riding, from 2,111 to 2,753 (Leeds C.B. 476, Sheffield C.B. 348), 466 in Essex, from 2,170 to 2,636 (Ilford M.B. 317, Dagenham M.B. 301, Hornchurch U.D. 296), 343 in Kent, from 804 to 1,147 (Maidstone M.B. 146), 289 in Middlesex, from 1,425 to 1,714 (Harrow M.B. 212, Hayes and Harlington U.D. 151, Tottenham M.B. 141), 223 in Surrey, from 881 to 1,104 (Woking U.D. 148, Croydon C.B. 126, Sutton and Cheam M.B. 111), 214 in Hertfordshire, from 432 to 646 (Hemel Hempstead M.B. 160). The largest decline in the number of notifications of scarlet fever was 33 in Yorkshire West Riding, from 144 to 111. The largest fluctuations in the trends of whooping-cough were a fall of 32 in Yorkshire West Riding, from 87 to 55, and a rise of 77 in Hertfordshire, from 4 to 81, due to an outbreak with 80 notifications in Stevenage U.D. 5 cases of diphtheria were notified, being 3 more than in the preceding week; 2 cases were notified in the cities of Liverpool and Birmingham.

The 11 cases of poliomyelitis were all paralytic and the notifications were 1 fewer for paralytic and 6 fewer for non-paralytic cases than in the preceding week. The largest returns were Lancashire 3 (Liverpool C.B. 2) and Hampshire 3 (Southampton C.B. 2).

The largest variations in the outbreaks of dysentery were an increase of 103 in Lincolnshire and a decrease of 106 in Yorkshire West Riding. The chief centres of dysentery during the week were Lincolnshire 258 (Grimsby C.B. 138, Boston M.B. 47, Cleethorpes M.B. 43, Glanford Brigg R.D. 17), Glamorganshire 215 (Cardiff C.B. 107, Barry M.B. 46, Rhondda M.B. 38, Llantrisant and Llantwit Fardre R.D. 13), Yorkshire West Riding 149 (Leeds C.B. 56, Bradford C.B. 44, Baildon U.D. 13), London 88 (Greenwich 22, Deptford 12, Islington 11, Wandsworth 11), Lancashire 66 (Manchester C.B. 25, Liverpool C.B. 14, Blackburn C.B. 11), Warwickshire 62 (Coventry C.B. 37, Birmingham C.B. 11), Yorkshire East Riding 52 (Kingston-upon-Hull C.B. 46), Surrey 44 (Coulsdon and Purley U.D. 16, Croydon C.B. 11), Cheshire 41 (Bebington M.B. 34), Staffordshire 41 (Kidsgrove U.D. 19, Stoke-on-Trent C.B. 10), Middlesex 40 (Tottenham M.B. 23), Nottinghamshire 37 (Beeston and Stapleford U.D. 23), Essex 36 (Walthamstow M.B. 13), Northumberland 33 (Newcastle-upon-Tyne C.B. 10, Morpeth R.D. 10); Hampshire 29 (Romsey M.B. 13), Berkshire 29 (Maidenhead M.B. 15).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 7** (No. 5) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	2	0	3	0		2	0	4	0	1
Dysentery	1,294	92	127	13	9	964	137	159	8	3
Encephalitis, acute	2	1		0		3	0		0	
Enteric fever:										
Typhoid	0	0	0	0		2	0	1	0	
Paratyphoid	10	1	0	0		4	0	1 (B)	0	5 (B)
Food-poisoning	129	13	4	0		145	14	51	0	
Infective enteritis or diarrhoea under 2 years				16	40				5	25
Measles*	22,170	1438	630	330	944	3,473	56	77	41	12
Meningococcal infection	28	7	13	2	3	26	4	14	1	
Ophthalmia neonatorum	29	4	4	0		27	1	1	0	
Pneumonia†	943	99	563	8	4	909	80	356	19	8
Poliomyelitis, acute:										
Paralytic	12	0	1	0	2	4	1	1	1	1
Non-paralytic	6	0	1			7	1			
Puerperal fever:§	218	37	9	0		239	41	6	0	
Scarlet fever	1,389	75	63	35	38	880	56	80	22	19
Tuberculosis:										
Respiratory	504	65	85	14		619	69	133	16	
Non-respiratory	47	2	11	4		63	3	23	6	
Whooping-cough	758	26	45	87	177	645	41	35	7	11

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	2	0		0		3	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		1	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	0	0	0	15	0	0	0	2
Influenza	144	10	12	0	0	204	15	3	0	1
Measles		1	1	0	0		0	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	986	95	66	21	8	1,086	81	40	37	20
Poliomyelitis, acute	2	1		0	0	3	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	123	9	15	0	9	115	6	17	3	5
Non-respiratory		0	1	0	1		0	1	0	0
Whooping-cough	1	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	354	37	38	5	11	427	32	39	10	19
Deaths (excluding stillbirths)	13,692	1241	996	160	188	14,138	1104	809	199	237
LIVE BIRTHS	14,692	1245	939	254	384	14,704	1203	1083	235	392
STILLBIRTHS	341	34	21			330	37	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Oxford Chair of Pharmacology.—Professor W. D. M. PATON, F.R.S., professor of pharmacology at the Royal College of Surgeons, has been appointed to the chair of pharmacology at Oxford from October 1. He succeeds Professor J. H. BURN, F.R.S., who has occupied the chair since 1937. Professor Paton graduated in 1938 at Oxford with first-class honours in animal physiology, proceeding B.M., Ch.B. in 1942. After house appointments at University College Hospital, London, he became pathologist at the King Edward VII Sanatorium. From 1944 to 1952 he was a member of the scientific staff of the National Institute for Medical Research. In the latter year he was appointed reader in applied pharmacology at University College and University College Hospital Medical School. In 1954 he was appointed to his present chair at the Royal College of Surgeons, of which he is the first occupant. With Professor E. J. Zaimis, he was responsible for the discovery of the methonium compounds. In 1956 Professor Paton was elected F.R.S. for his distinguished work in this field.

Day Hospital Research Grant.—The Nuffield Provincial Hospitals Trust has made a research grant of £12,000 to Cheadle Royal Hospital to set up an experimental day hospital accommodating from 40 to 60 patients with various types of nervous illness. Research will be carried out into the effect on day patients of working in a "sheltered workshop" in which they are employed for their own profit in making commercial articles. The centre will draw from a population of about one million living within an eight-mile radius.

College of General Practitioners: Butterworth Gold Medal.—This award is presented annually to the College of General Practitioners by Butterworth & Co., the medical publishers, for an essay by a member or associate of the College on a subject connected with general practice. The subject of this year's essay is "The Child is Father of the Man." Essays, identified by motto only (with the author's name and address in a sealed envelope), and not exceeding 10,000 words, should be submitted to the Chairman, Awards Committee, the College of General Practitioners, 41, Cadogan Gardens, Sloane Square, London, S.W.3, by September 19.

"International Journal of Radiation Biology."—The first issue of this new British journal has recently been published. It is a quarterly, international in character, which proposes to "bring together all interests concerned with the biological effects of ionizing radiations." Papers may be submitted in French and German as well as in English, and will be summarized in these two languages. The editor is Dr. W. M. DALE (Christie Hospital and Holt Radium Institute, Manchester) and the journal has an international editorial board. The publishers are Taylor and Francis, Ltd., Red Lion Court, Fleet Street, E.C.4 (American agent: Academic Press, Inc., 111, Fifth Avenue, N.Y. 3, New York), and the annual subscription is £3 15s. (5,155 fr., DM. 44, $10.50).

"Intermedica."—The first British edition of *Intermedica*, the journal of the International Federation of Medical Student Associations, has now been published. It will appear at least twice a year and it is hoped that the next issue will be published in English, French, and German. The support of Roche Products Ltd. has made publication possible, and the journal is free to all medical schools within the Federation and also to many schools in non-member countries. Inquiries and original articles should be sent to the Editor, Intermedica, British Medical Students' Association, B.M.A. House, Tavistock Square, London, W.C.1.

Merseyside Medical Art Society Exhibition.—Exhibitors who propose to submit pictures through the North of England centre for the art exhibition at the B.M.A. Joint Annual Meeting at Edinburgh this year are invited to take part in the Merseyside Medical Arts Society Exhibition to be held in Liverpool from March 16 to 21. Pictures for the Liverpool exhibition should reach Professor B. G. MAEGRAITH, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, 3, by March 10. There will be a hanging fee of 7s. 6d. The closing date for submission for the Edinburgh exhibition is March 31.

Scottish Air Ambulance.—In future no one in Scotland will be out of range of air ambulance cover, said Lord FORBES, Minister of State for Scotland, at a press conference in Aberdeen earlier in the month. For the first time patients in the Outer Hebrides, the Shetlands, Fair Isle, Foula, and remote corners of the mainland can now be flown out by Service helicopter when speed may mean the difference between life and death. Helicopter service is already available on this basis to the other Scottish islands, and these islands will now be able to call on it for seriously ill cases as well. The air ambulance service lifts about 300 patients a year, of whom only a few are what it describes as "life-or-death" emergencies.

New Rhodesian Hospital.—Work will start early next year on the first stage of the £2m. European hospital for Salisbury, announced the Minister of Health for the Federation of Rhodesia and Nyasaland, Mr. B. D. GOLDBERG, on February 1. A radiotherapy block will probably be completed by the end of 1959, and the first part of the new hospital will have accommodation for 220 patients.

Space Research.—A committee has been formed to advise the U.S. Armed Forces on any matter concerning the biological or medical aspects of space exploration. It will be known as the Armed Forces–National Research Council Committee on Bio-Astronautics, and has been organized by the National Academy of Sciences–National Research Council. The congressional charter of this council, signed in 1863 by President Abraham Lincoln, calls upon the Academy to advise the Government, on request, in matters of scientific and technical interest. Its president is Dr. DETLEV W. BRONK.

Medical Defence Union.—Dr. ROBERT FORBES, who has been secretary of the Union for 24 years, is to retire on May 31. He will be succeeded by Dr. PHILIP H. ADDISON, the present deputy secretary. Dr. J. W. BROOKE BARNETT will continue to hold the same post, and Dr. D. F. ROBB will be appointed to the staff as assistant secretary as from March 2.

Narcotics Research.—The Nuffield Foundation has awarded a 1959 travelling fellowship for home civil servants to Mr. T. C. GREEN, of the Home Office, the United Kingdom representative on the U.N. Narcotics Commission. He will study all aspects of the problem of dangerous drugs in Aden, India, Pakistan, Singapore, Malaya, Hongkong, Siam, and Canada.

Toothpaste Claims. — The Independent Television Authority has announced that television toothpaste advertisements which make misleading claims are to be withdrawn or modified. This is the result of a recommendation from the advertising advisory committee of the I.T.A. following representations from the British Dental Association.

R.C.S., Ireland.—The College held its Charter Day dinner on February 14. Before the dinner the President, Mr. T. G. WILSON, admitted Sir ERNEST FINCH and Sir ARCHIBALD MCINDOE to the honorary fellowship of the College. Mr. R. A. STONEY, the senior member of council, was presented with his portrait, painted by Mr. DAVID HONE. On February 20 fellowship of the College was conferred on Mr. GEAROID LYNCH.

Durham University.—Dr. C. A. GREEN has been appointed to the chair of bacteriology, and Mr. G. L. HOWE to the chair of oral surgery.

London University.—Mr. G. L. SLACK, senior lecturer in preventive dentistry in the University of Liverpool, has been appointed to the University chair of dental surgery tenable at the London Hospital Medical College.

Sheffield University.—At a meeting of the council on February 20, the following appointments were made: W. A. J. CRANE, senior lecturer in pathology; T. G. KERSHAW, assistant lecturer in physiology; and R. RASTALL, honorary lecturer in dental surgery (part-time).

"Natural Causes."—This play, by Mrs. VERA COLEBROOK, was first produced in November, 1958, at the Hovenden Theatre Club. It will be played again, for one night only, on March 16 at the Arts Theatre, London.

Professor W. S. Craig, professor of paediatrics and child health in the University of Leeds, is to lecture and take part in clinical work in Bergen and Oslo under the auspices of the British Council.

COMING EVENTS

"Manipulation."—A series of lectures under this broad heading will be held at B.M.A. House, Tavistock Square, on April 4, May 2, June 6, and July 4, from 9.30 a.m. to 5.30 p.m. Further information from Dr. A. STODDARD or Dr. GUY BEAUCHAMP, 119, Harley Street, London, W.1.

I.S.T.D. Change of Date.—"Problems of Adoption," Bracklesham Bay Hotel, Chichester, Sussex, will now be held on May 1–3.

Brighton Technical College, School of Pharmacy.—Symposium on "The Operation of Sterilizing Autoclaves" on May 9. Details from Dr. J. C. PARKINSON, School of Pharmacy, Technical College, Brighton, 7.

European Society of Haematology.—The seventh congress will be held at Bedford College, London, from September 7 to 12. The Société Internationale de Transfusion Sanguine will arrange sessions in conjunction with the congress. Subjects for discussion include anaemia, leukaemia, disorders of blood coagulation, bone-marrow transplantation, and haemoglobinopathies. Further information from Dr. E. NEUMARK, St. Mary's Hospital, London, W.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, February 28

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Addenbrooke's Hospital, Symposium in Orthopaedics and Physical Medicine. Morning, 10.30 a.m., Mr. L. W. Godfrey: Tenosynovitis; Mr. R. W. Butler: Trauma in Infancy and Early Childhood; Mr. E. S. Jamieson: Recent Advances in the Surgery of Tuberculosis of Bones and Joints. Afternoon, 2.15 p.m., "Any Questions?" Mr. T. J. Fairbank: Osteoarthritis of the Hip; Dr. R. R. P. Hayter: Scope of Physical Medicine.

Monday, March 2

DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS.—At Royal Society of Medicine, 8 p.m., Dr. W. A. H. Stevenson: Uses and Abuses of Hypnotism.

GUY'S HOSPITAL.—5.15 p.m., endocrine demonstration by Dr. A. W. Spence: Radiological Appearances in Endocrine Disease.

INSTITUTE OF PSYCHIATRY.—5.30 p.m., public lecture by Dr. W. S. Feldberg, F.R.S.: A Physiological Approach to the Problem of Loss of Consciousness.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Guest lecture by Dr. Brian Ackner: Hysteria.

Tuesday, March 3

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor A. A. Miles: Mediators of the Vascular Phenomena of Inflammation.

COLLEGE OF GENERAL PRACTITIONERS: SOUTH-EAST SCOTLAND FACULTY.—At 7, Drumsheugh Gardens, Edinburgh, 8.30 p.m., Pfizer Postgraduate Lecture by Sir Heneage Ogilvie: Anxinoia—Suspension of Judgment.

INSTITUTE FOR THE STUDY AND TREATMENT OF DELINQUENCY.—7 p.m., Dr. Melitta Schmideberg: Practical Problems in the Handling of Offenders.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. W. Frankland: Allergy and Dermatology.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., clinical lecture by Professor F. C. Ormerod: Histochemistry of the Inner Ear.

LONDON UNIVERSITY.—At King's College, Strand, W.C., 5.30 p.m., special university lecture in philosophical studies by Professor J. Hyppolite (Paris): La Psychanalyse et la Philosophie Contemporaire.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Dr. Lars PH. Bengtsson: Hormonal Control of Pregnancy and Labour in the Human.

Wednesday, March 4

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Miss B. M. Partridge: New Cultural Techniques for the Investigation of Pathogenic Fungi.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. J. Prime: Factors Limiting Exercise Tolerance.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., clinical pathological conference by Dr. I. Friedmann, Dr. D. A. Osborn, and Dr. A. L. Jeanes.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. D. E. H. Phillips: Enlarged Prostate: Pathological Considerations.

IRISH GERONTOLOGICAL SOCIETY.—At Moyne Institute, Trinity College, Dublin, 8.30 p.m., Dr. P. D. J. Holland: Hospital Staphylococcus in Old Age and Infancy.

LIVERPOOL MEDICAL INSTITUTION.—Joint meeting with Manchester Medical Society at Manchester University, 5 p.m., Mr. Philip Hawe, Dr. W. H. R. Cook, and Dr. W. Kulke: Current Trends in the Management of Thyroid Disorders.

LONDON UNIVERSITY.—At King's College, Strand, W.C., 5.30 p.m., special university lecture in philosophical studies by Professor J. Hyppolite (Paris): La Psychanalyse et la Philosophie Contemporaire.

MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., Mr. A. J. H. Rains: Life and Death of Cholecystectomy.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. Robert White: Immune Cellular Reactions.

Thursday, March 5

ALFRED ADLER MEDICAL SOCIETY.—At Royal Society of Medicine, 8.15 p.m., Dr. Spencer Paterson: Use of Physical Methods in Psychotherapy.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor D. F. Cappell: Iron Metabolism.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Mr. Robert Brain: Oesophageal Replacement.

LIVERPOOL MEDICAL INSTITUTION.—At Whiston Hospital, 2.30 p.m., clinical demonstration.

ROYAL SOCIETY OF HEALTH.—At Town Hall, Huddersfield, 10 a.m., Dr. R. G. Davies: Ten Years After (Aspects of the N.H.S. Act as they appear ten years after its inception in 1948); Symposium by Dr. M. Haynes, Mr. Dennis Drake, and Miss M. E. Porritt: Changes in the Work of the Health Department Over the Last Ten Years.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, 5 p.m., Mr. D. H. Patey: Present Position of Surgery of the Parotid.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: psychiatry.

SOCIETY OF CHEMICAL INDUSTRY: MICROBIOLOGY GROUP.—At 14, Belgrave Square, London, S.W., 6.15 p.m., Professor G. F. Gause (Moscow): Microbes' Contribution to Cancer Research.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Nurses' Hall, West London Hospital, 7.30 for 8 p.m., dinner meeting. Professor A. Haddow, F.R.S.: Chemotherapy of Malignant Disease.

Friday, March 6

INSTITUTE FOR THE STUDY AND TREATMENT OF DELINQUENCY.—7 p.m., Dr. Melitta Schmideberg: Practical Problems in the Handling of Offenders.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. B. Russell.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. N. C. Oswald.

INSTITUTION OF ELECTRICAL ENGINEERS: MEDICAL ELECTRONICS DISCUSSION GROUP.—5.30 for 6 p.m., discussions. Mr. H. S. Wolff: Potted Histories of Instruments Designed for Medical Purposes. Dr. R. G. Willison: Co-ordination of Research in Medical Electronics.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Dr. C. H. Edwards: Some Recent Advances Concerning Cerebral Vascular Disease.

JAMES YEARSLEY LECTURE IN OTOLOGY.—At Royal Society of Medicine, 5.15 p.m., Dr. Karsten Kettel (Denmark): Surgery of the Facial Nerve in Atraumatic Facial Palsies.

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., short papers by Mr. J. G. Dumoulin, Dr. M. B. Feil, Dr. W. A. Lister, and Dr. Robert Walker.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Professor A. W. Wilkinson: Some Principles in Neonatal Surgery. 4 p.m., Professor W. S. Peart: Some Aspects of Carcinoidosis.

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Faculty of Physicians and Surgeons of Glasgow, 8.30 p.m., Dr. J. Fulton Christie and Dr. W. Blair: Otitis Media.

UNIVERSITY OF WALES.—At Reardon Smith Lecture Theatre, Park Place, Cardiff, 8 p.m., Sir James Paterson Ross: The Scientific Approach to Surgery.

Saturday, March 7

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—11.30 a.m., film by Professor Horst Wullstein (Würzburg): Ciliary Action of Living Nasal Mucous Membrane.

Sunday, March 8

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, 2 p.m., symposium. Dr. R. Arden Jones: Pulmonary Embolism; Dr. D. M. T. Gairdner: Enuresis; Mr. W. H. Carlisle: Surgical Pathology and Treatment of Gravitational Ulcers of the Leg; Dr. J. Marks: Anticoagulant Therapy.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Camac.—On February 12, 1959, at Burton Nursing Institute, to Joyce (formerly Swift), wife of Dr. J. Camac, a daughter—Sandra Gail.

DEATHS

Bardsley.—On February 1, 1959, at his home, 43, Oxford Road, Birkdale, Lancs, Henry Bardsley, M.R.C.S., L.R.C.P.

Carmichael.—On February 1, 1959, at 8, Dan-y-Coed Road, Cyncoed, Cardiff, Robert McLuckie Carmichael, M.B., Ch.B., aged 59.

Gellatly.—On February 3, 1959, at Thorncroft, South Hill Avenue, Harrow, Middx, Norman Croll Gellatly, M.D.

Hill.—On February 5, 1959, Kathleen Mary Hill (formerly Parker), M.B., B.S., late of Niger Mission, Nigeria, aged 32.

Preiss.—On January 29, 1959, at Colindale Hospital, London, N.W., Arnost Ernest Preiss, M.D., D.M.R.E., of Rosemont Court, Rosemont Road, London, W.

Sankey.—On February 1, 1959, at The Cottage, Sandy Lane Road, Charlton Kings, Cheltenham, Glos, Charles Fox Octavius Sankey, C.B.E., M.B., B.S., Surgeon Rear-Admiral, R.N., retired, aged 73.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

B.C.G. Vaccination in Pregnancy

Q.—*Is there any danger in giving B.C.G. to a pregnant woman with a negative Mantoux ?*

A.—There is no danger in inoculating a Mantoux-negative pregnant woman with B.C.G. In fact, this has often been done without any harm to either mother or foetus.

Corticosteroids in Disseminated Sclerosis

Q.—*What is the value of A.C.T.H., cortisone, or prednisone in the treatment of acute episodes in disseminated sclerosis ? Which is the drug of choice ? In what dosage, and for how long, should it be given ?*

A.—Any conclusions about whether A.C.T.H. or cortisone or its derivatives are effective methods of treatment for disseminated sclerosis must at present be regarded as highly tentative. Alexander, Berkeley, and Alexander[1] believe that A.C.T.H. is effective while cortisone is not, but it is difficult to see why this should be so. They recommend that 40 units of A.C.T.H. should be given by intravenous drip 8-hourly for 10 days ; then 60 units of A.C.T.H. gel should be given intramuscularly 12-hourly for 10 days. Thereafter the dosage should be reduced by 20 units every 3–5 days until a maintenance dose of 20–40 units 2–3 times weekly is reached. This treatment, according to the authors, should be continued indefinitely, and it is claimed that it reduces the frequency of relapses. Most neurologists in this country would not at present agree with the advisability of giving such treatment over a long period, but many now feel that a course of A.C.T.H., as outlined above, may reasonably be given during an acute episode of disseminated sclerosis and should then be continued for some 2–4 months, depending upon the clinical response. Others, taking the view that A.C.T.H. is no better than cortisone or similar remedies in such cases, would prefer prednisone or prednisolone in an initial daily dosage of 60 mg. daily for 4–5 days, reducing to 40 mg. daily for 1–2 weeks and thereafter reducing gradually to a maintenance dosage of 10–15 mg. daily, again continuing for some 2–4 months.

REFERENCE

1 Alexander, L., Berkeley, A. W., and Alexander, A. M., *J. Amer. med. Ass.*, 1958, **166**, 1943.

Eyes and Furnace Radiation

Q.—*What type of goggles and filter lenses are most suitable for workers in a lamp-black furnace ?*

A.—In deciding whether a hazard to the eyes of workers engaged on this process exists, it is helpful to know the spectrum of radiation emitted and the energy flux of such radiations. The spectral emission of this creosote fuel is likely to contain radiations of 8,000 Å units upwards.[1] Heat cataract is caused by infra-red rays, particularly the shorter wavelengths from 8,000 to 12,000 Å units.[2] To produce definite lens changes an energy flux of about 0.12 cals./cm.²/sec. is required.[3,4] Investigations in an iron foundry where the energy flux was 0.02–0.1 cals./cm.²/sec. revealed only minimal changes in the posterior capsular region of the lens,[5,6] although there was no subjective disturbance. Similar findings were reported from glass works where the maximum energy flux was 0.38 cals./cm.²/sec.[7]

For protection from infra-red radiation, the British Standards booklet *Green Protective Spectacles and Screens for Steel-Works Operatives*[8] should be consulted. The green glass provides better protection than the cobalt-blue glass often traditionally worn.[9] A heat-absorbing clear glass is manufactured, and is intended primarily for use in the heat filters of projectors. It is at present under trial in industrial conditions.[10]

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3 Goldmann, H., *Ann. Oculist*, 1935, **172**, 13 (quoted by J. E. Coates and G. F. Keatinge).
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5 Keatinge, G. F., Pearson, J., Simons, J. P., and White, E. E., *A.M.A. Arch. industr. Hlth*, 1955, **11**, 305.
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Blighted Ovum

Q.—*After ten weeks' amenorrhoea with symptoms of pregnancy, a patient miscarried, passing what appeared to be a foetus with membranes intact. It later proved to be a cyst 2 in. (5 cm.) in diameter, thick-walled and fluid-filled, but without a foetus. Was this patient pregnant, and, if so, what had become of the foetus ?*

A.—The description of the specimen extruded from the uterus is that of a "blighted ovum." Although often unrecognized because of incomplete examination of the products of conception, this is a common condition and a frequent cause of abortion. Blighted ova vary in detail. Even though the membranes are normal and the sac distended with fluid, the foetus may be completely absent or may be represented by a rudimentary shapeless structure. The body stalk is often present even though the foetus is absent. These defects manifest themselves very early in the pregnancy and presumably arise because of an error in the development of the inner cell mass, the trophoblast meanwhile continuing to form reasonably normally. In other words, the absence of the foetus is explained by its failure to develop rather than by its death and subsequent absorption. The adverse factor which operates is unknown and could presumably be either genetic or environmental. Full and illustrated accounts of blighted ova are to be found in the larger textbooks such as *Williams' Obstetrics*,[1] and in *Spontaneous and Habitual Abortion*.[2]

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1 *Williams' Obstetrics*, edited by N. J. Eastman, 1956. Appleton-Century, New York.
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Correction.—We regret that the name of Dr. A. D. D. BROUGHTON, M.P., was wrongly given in our parliamentary report on January 31 (p. 310) as Dr. Donald Broughton.

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